Vitamin D Physiology and its Importance in Dairy Cattle: A Review

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Abstract

High milk yields make considerable demand on calcium and phosphorus metabolism in the dairy cow. Vitamin D plays a major role in calcium metabolism and, hence, indirectly in phosphorus metabolism. Too often vitamin D has been neglected in current dairy cow nutrition. Several factors including high energy rations, high milk production, and use of exotic rations indicate a need to reevaluate vitamin D nutrition for high producing cows.

In rations with sufficient calcium, adequate vitamin D promotes positive body balance, but natural sources may provide insufficient vitamin D in many high-energy, low-roughage rations. Recent discoveries of vitamin D metabolites and their role in calcium metabolism have spurred related basic research. Knowledge of vitamin D/calcium metabolism may have practical value in treating and preventing parturient paresis as well as in nutrition per se. In addition, vitamin D may be related to reproductive performance via enhanced psychic estrus expression. Finally, the knowledge of vitamin D in contemporary dairy cattle nutrition is simply less complete than many believe.

Introduction

Discoveries of Steenbock (66) and Hess and Weinstock (34) began mitigating rickets as a major medical problem in man and other animals. Their experimental induction of antirachitic properties to food sterols by ultraviolet irradiation equated these properties with the fat-soluble entity named vitamin D by McCollum et al. (46). Mellanby (47) earlier had produced and subsequently cured or prevented rickets in dogs by feeding cod-liver oil, but he incorrectly ascribed the antirachitic effect to vitamin A.

Huffman (41) related the knowledge to calves by noting that sunshine counteracted the effects of a rachitic diet. Considerable work in both preventing and producing rickets in calves followed (2, 4, 63). Rickets is rarely a contemporary problem in calves or adult cattle so severe deficiencies are considered briefly.

DeLuca (20) defined rickets as a condition in which calcification does not keep pace with synthesis of bone organic matrix. Bechtel et al. (4) summarized the generally accepted views on macroscopic and microscopic abnormalities in calf rickets while Craig and Davis (19) commented specifically on dental and oral cavity conditions in rachitic calves.

Nearly the sole investigations of acute vitamin D deficiency in mature dairy cows are those of Wallis (70, 71). After being maintained on a vitamin D deficient regimen, cows exhibited lower plasma calcium and phosphorus concentrations (one-half and one-fifth normal, respectively), bone breakage, decreased milk production, and many of the symptoms of rachitic calves. Although Wallis (71) observed bone fragility (osteomalacia) and the failure of all animals to show estrus, he did not relate them directly to vitamin D deficiency. Many others, including Liu et al. (44) and Harrison et al. (30), have established that osteomalacia results from vitamin D deficiency in adult animals. Wallis found feeding cod-liver oil and viosterol remitted symptoms of vitamin D deficiency in cows not yet exhibiting extreme skeletal deformities. After these studies, interest in vitamin D in dairy cattle nutrition waned. Recent advances in vitamin D physiology, possible relationships of vitamin D to processes heretofore thought unaffected by the vitamin, and stress imposed on high-producing cows make it desirable to review knowledge of vitamin D in dairy-cattle nutrition.

Chemistry and Activity of Vitamin D and its Metabolites

Several compounds have different amounts of vitamin D activity. Ultraviolet irradiation of Δ5,7 sterols results in isomerization reactions that yield the basic vitamin skeleton (33). Before 1966, six main compounds having calcifying properties had been isolated.
With an assigned vitamin D activity of 100% for vitamin D₃ (cholecalciferol) in the rat and chick, vitamin D₂ (ergocalciferol) has 100% and 10%, and vitamin D₄ has 50 to 75% and 20% activities in the rat and chick, respectively (53, 55). Relative activities of the other vitamin D compounds are even less. What for a time was considered the ultimate functional form of vitamin D, 25-hydroxycholecalciferol (25-HCC), was isolated from bone, liver, and blood serum (common sites of vitamin D) and characterized by Lund and DeLuca (45). This form is 1.4 times as active as vitamin D in curing rickets (5). Calcium transport in perfused rat intestine has been stimulated by moderate amounts of 25-HCC while larger doses of cholecalciferol had little or no effect (57).

Corradino and Wasserman (16) did not confirm entirely Lund and DeLuca’s findings. In vitro synthesis of calcium binding protein (CaBP) was increased significantly in their study by including vitamin D₃ in the culture medium (0 μg in the control group to 13.5 μg in the vitamin D₃ group). Calcium uptake was increased only about 3.5%. However, they pointed out that the increase was highly reproducible. Dihydrotachysterol-2, a vitamin D₃ derivative, was nearly as potent as D₃ on a molar basis. The 25-HCC was two to three times more active than D₃ while cholesterol, 7-dehydrocholesterol, ergosterol, hydrocortisone, estradiol, and testosterone were not effective. Of the steroids, only those active in vivo were active in vitro. Only about 1% of vitamin D₃ was converted to 25-HCC. They concluded that intestinal mucosa exhibits a relative, rather than an absolute, specificity toward vitamin D-related sterols.

Still another metabolite of cholecalciferol has been isolated from chick intestinal mucosa. Myrtle and Norman (49) named that metabolite 4B and assumed it was the same as the compound designated peak V by Cousins et al. (17, 18) and Gray et al. (27) (same laboratory). Lawson et al. (43) reported a similar compound with faster action and greater potency than for 25-HCC. Norman et al. (56) and Omdahl and DeLuca (60) since have identified that metabolite (4B and peak V) as 1,25-dihydroxycholecalciferol (1,25-dihC). Cholecalciferol and 25-HCC both cause maximum calcium transport 24 to 48 h after being administered. Conversely, 1,25-dihC has a lag time of 9 h and is 13 times as active as cholecalciferol (49). DeLuca, Kodicek, and Norman (25, 27, 56, 60) indicate that vitamin D₃ is converted to 25-HCC in the chick liver, is further hydroxylated to 1,25-diHCC in the kidney, and finally is active as 1,25-diHCC in the intestinal mucosa and bone. Rats fed a low phosphorus diet supplemented with 25-HCC synthesized more 1,25-diHCC and had more intestinal calcium transport activity than rats fed the same diet but with adequate phosphorus (68). DeLuca (21) and Wasserman and Corradino (74) have more details on recent discoveries concerning metabolites of vitamin D.

**General Physiology and Mode of Action**

1) **Intestinal absorption and excretion.** Absorption of ingested vitamin D occurs, with the aid of bile salts, primarily in the lower third of the small intestine. Being lipid soluble, vitamin D enters the lymphatic system and then the blood stream. In the lymphatic system, most of the vitamin is carried in the chylomicron fraction. Excretion of vitamin D is into the feces via bile (33).

2) **Blood transport and tissue distribution.** After dosage, vitamin D is associated initially with chylomicrons and lipoproteins in rat blood (62, 65). As time passes, the vitamin increasingly associates with the α-globulins. That fraction appears to be the main carrier of physiological quantities of vitamin D and 1,25-diHCC. Chen and Lane (11) have shown that it is tightly bound. Vitamin D is typically localized in four organs: liver (as free vitamin D), mucosa of the small intestine, bone, and in the first third of the kidney proximal tubule (7, 42, 52, 53). All those organs except the liver turn over phosphate, citrate, and calcium faster than most other tissues. Conversion to 25-HCC and the resulting association with α-globulins occurs in the liver (40). It seems clear, at least regarding its effects in the intestine, that 25-HCC is converted to 1,25-diHCC in the kidney (27); in this form, vitamin D is transferred to the intestine where it is the most active form (27, 43, 49).

3) **Action in the intestine and bone.** Less contemporary ideas and observation concerning vitamin D’s methods of action should not be ignored. Some older studies have merit and others, even though not biologically basic, may still indicate new approaches. Vitamin D increases calcium absorption and bone turnover. Carlsson et al. (10) found that serum citric acid decreased slightly, then greatly increased in young rats given vitamin D. Citric acid content of bones and incisors also increased. Fluctuations in serum citric acid were paralleled by
changes in serum calcium and phosphorus. These workers stated, "The evidence seems to be against the assumption that the effect of vitamin D on citric acid metabolism is secondary to its action on mineral metabolism. By accelerating the production of citric acid in the bones, the solvent action of the vitamin on bone salts is thought to find its explanation."

Gaster et al. (26) also reported that rats supplemented with vitamin D had more citric acid per unit of fat free bone. They concluded that vitamin D added to low calcium diets does not increase calcification but increases calcium turnover. Neuman and Neuman (51) suggested that bone crystals and extravascular fluid in contact with bone are not representative of equilibrium. They postulated instead a hydrogen ion gradient between the fluid and the crystals, which fits well with the citrate-citric acid observations.

Active transport of Ca\(^{45}\) by the intestinal mucosa depends on vitamin D (84). Both absorption and utilization of calcium are increased by vitamin D (8). Coates and Holdsworth (12) noted that calcium absorption was twice as great in chicks supplemented with vitamin D\(_3\) as in rachitic controls, but chicks fed a single oral dose of vitamin D and those dosed before hatching did not differ in calcium absorption. Calcium absorption in vitro was enhanced by chick bile.

More recent work indicates that 1,25-diHCC is selectively localized in the nucleus of intestinal mucosal cells (31, 32) where it actively facilitates synthesis of CaBP (25, 27, 49). Other reports have linked vitamin D administration less directly with facilitating or stimulating CaBP synthesis and calcium absorption (29). Most likely CaBP synthesis is promoted by 1,25-diHCC influencing the genetic machinery of the cell, but there are unresolved questions. A well-known protein synthesis inhibitor, actinomycin D, repressed the action of vitamin D on intestinal calcium absorption (54, 75), but that repression was not toxicity per se (76). Hypercalcemia induced by pharmacological doses of vitamin D is also inhibited by actinomycin D (24), indicating that vitamin D may act on bone as it does in intestinal mucosa. DeLuca and Suttie (22) and Wasserman and Corradino (74) give more detailed information on basic vitamin D physiology.

**Vitamin D Requirements in Dairy Cattle**

In sharp contrast to copious basic work on the mode of action of vitamin D are the few reports on the vitamin D requirements of dairy cattle. It is reasonable to assume similar modes of action for vitamin D in the dairy animal, chick, and rat. However, specific peculiarities, i.e., high milk production, skin synthesis, ruminant digestion, and possible estrogen-mimicking effects in the dairy cow confound the situation and emphasize the lack of substantial data to establish requirements.

Colovos et al. (14) found that vitamin D deficiency seriously impaired calf growth, health, and feed efficiency. Protein digestion, nitrogen retention, and ash digestion were diminished by low vitamin D intake, but digestion of dry matter, ether extract, crude fiber, nitrogen free extract, and energy were not affected. Efficiency of both protein and energy decreased. Basic metabolic rate increased, blood calcium, and phosphorus decreased, and blood alkaline phosphatase increased. Rasmussen (61) observed similar growth depression in rats.

Regarding manifestations of less severe vitamin D deficiencies, factors other than enhancing positive calcium and phosphorus balances should be examined. The vitamin's relationship to reproduction may prove to be of great practical consideration. Hignett and Hignett (39) observed increased fertility in cattle in good vitamin D status (determined by season rather than supplementation) compared with cattle on lower D intakes. Cohen (13) conducted experiments with 189 anestrus cows. He compared water-soluble crystalline vitamin D\(_3\) injections (5 to 10 million IU dose) with no treatment and with subcutaneous gonadotropin injections. More cows exhibited estrus in the D-treated groups (p < .025 compared with no treatment and p < .05 compared with gonadotropin). Cohen stated that in the observed situations, vitamin D\(_3\) had estrogenic activity. He also noted that D\(_3\) administration terminated broadness in turkeys (13). Hafez (28) stated that vitamin D indirectly affects female fertility, by affecting calcium and phosphorus utilization. Earlier conception in cows given 300,000 IU supplemental vitamin D weekly was reported by Ward et al. (73). They suggested that vitamin D may alter hormonal concentration and/or expression and thereby account for a higher incidence of observed estrus among supplemented cows. That would account for the shorter average calving interval in cows receiving supplemental D as the improvement apparently was from detecting otherwise missed estruses rather than from shorter calving-to-first estrus intervals. That is in line with the failure of vitamin D deficient cows to show estrus reported by Wallis.
A precipitous blood-calcium decline occurs in parturient paresis. Attempts to prevent the decline have involved two basic approaches. Some researchers feed low calcium, high phosphorus (6) rations. Hibbs et al. (35, 36, 37) used another approach, that of feeding large amounts of vitamin D. Both methods were expected to stimulate parathyroid activity. Heretofore, parathyroid inadequacy and/or lag in activity were presumed to depress blood calcium at parturition. Lactation and parturition tax the parathyroid (9), but Stott and Smith (67) found no evidence of parturient paresis in cows calving after parathyroidectomy performed immediately prepartum or in mid-lactation.

Hibbs and Pounden (37) fully prevented parturient paresis by feeding 30 million IU of vitamin D daily at least 3 but no more than 7 days prepartum. Normal serum calcium and phosphorus were maintained during the critical prepartum and postpartum periods.

Conrad and Hansard (15) investigated the effects of 5 million units of vitamin D given to cows daily for 5 days. Average true digestibility of calcium increased from 48% for the controls to 70% for supplemented cows. Endogenous fecal calcium excretion decreased from 2.27 g per day for controls to 1.64 g per day for vitamin D-supplemented cows. The calcemic effect of the supplement in cows was not seen in young calves, but older calves retained approximately three times as much calcium with increased Ca\textsuperscript{45} deposition in areas of bone growth.

Data on vitamin D toxicity in dairy cattle are scarce. Duncan and Huffman (23) produced toxicity in milk fed calves with massive daily doses of viosterol. Hibbs and Pounden (37) reported toxicity in cows fed 30 million IU vitamin D daily for 21 to 30 days. However, cows on the metabolized vitamin D milk program averaged 500,000 IU vitamin D daily with no harmful effects (1).

Injections of 25-HCC have been unsuccessful in treating parturient paresis (58); however, as a preventive, 4 mg 25-HCC injected intramuscularly (72 h to 10 days before parturition) significantly reduced the incidence of parturient paresis (59). The greater activity of this compound than cholecalciferol and its lag time, 24 to 48 h for maximum calcium transport, serve to explain its value as a preventive and its failure as a treatment.

In an experiment designed to ascertain effect of vitamin D on cows' ability to mobilize calcium, Muir et al. (48) used ethylenediaminetetraacetate (EDTA) to chelate blood calcium and thus challenge calcium mobilization. With short infusion time, one-half recovery time was the same for vitamin D supplemented and control cows, but cows with a previous history of parturient paresis showed longer one-half recovery times. With more prolonged EDTA infusion, vitamin D-fed cows mobilized calcium one and one-half times better than controls. It was calculated that two and one-half times the original blood calcium was removed with the infusion, but in the short-time infusion, only one-half of the original calcium was chelated.

Vitamin D in the ration is recommended in the following amounts per kilogram of dry matter: 600 IU for calf milk replacer, 250 IU for calf starters, and 300 IU for milking cow rations, yet no vitamin D requirement is listed for animals weighing more than 200 kg (50).

Sources used in compiling those recommendations are sketchy at best for calves (3, 14, 63, 69) and even less substantial for mature cows (38, 71). Hibbs and Conrad (38), who fed 32,000 IU vitamin D per pound of concentrate, noticed no ill effects and slightly higher calcium retention in cows having positive phosphorus balances. Parturient paresis decreased in cows with a history of the disorder after feeding vitamin D. It may be undesirable to feed vitamin D at that rate to cows with no history of the disease. Wallis (71) dealt essentially with remission of deficiency symptoms. Field practices vary considerably, but some dairymen are supplementing rations with vitamin D. Heretofore many thought natural food-stuffs and skin synthesis furnished sufficient vitamin D for mature dairy cows. That may be, but variability, uncertainty, and lack of knowledge reduce confidence in their adequacy.

Ward et al. (72) demonstrated improved utilization of calcium by dairy cows receiving 300,000 IU supplemental vitamin D weekly in addition to that in the natural ration consisting of alfalfa hay and grain. Predictability of calcium balance from milk calcium and calcium and phosphorus intakes was enhanced by vitamin D supplementation as well as attaining positive Ca\textsuperscript{45} balance early in lactation in cows consuming adequate Ca. Those results support addition of vitamin D to dairy cattle rations as insurance against possible deficiency.

References


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