ABSTRACT

This paper describes the mechanism of calcium and phosphorus homeostasis in dairy cows in an effort to provide a clearer understanding of the rationale behind current management and supplementation practices. Specifically addressed is the need to keep prepartum dietary calcium intake at \(< 50\) g/d to minimize the incidence of milk fever. Also discussed is the need to increase National Research Council recommendations for postpartum dietary calcium from 2.7 to 3.4 g/kg milk. This is particularly important during the first 1 to 2 mo of lactation to maintain calcium balance.

INTRODUCTION

In common with other homeostatic controls, all vertebrates are able to regulate the concentration of calcium (Ca) in plasma with remarkable precision. In contrast, plasma phosphorus (P) is controlled less stringently. A general scheme of Ca and P metabolism is illustrated in Figure 1. Results of experiments involving intravenous injections of radiolabeled Ca and P suggest that they are in exchange in plasma with pools about 35 and 100 times larger, respectively, than the amount circulating in the blood (18, 50). Calcium and P are supplied to their pools through intestinal absorption and bone resorption. In the nonlactating, nonpregnant bovine, Ca and P exit the pool by feces, urine, and bone and also from the fetus and mammary gland in the case of pregnant, lactating animals. The maintenance of the extracellular Ca and P pools depends upon a balance between their entry and exit from these pools. Regulation of the Ca and P pools are under the influence of two potent calcitropic hormones — parathyroid hormone (PTH) secreted from the parathyroids and 1,25-dihydroxyvitamin D \([1,25-(OH)_2D]\), the metabolite of vitamin D produced in the kidney. This paper will describe the nutritional-endocrine interactions involved in the maintenance of Ca and P in plasma.

DISCUSSION

Vitamin D Regulatory System

The two major natural sources of vitamin D to ruminants result from photochemical conversion of 7-dehydrocholesterol to vitamin D3 in the skin or from plants as a result of photochemical conversion of ergosterol to vitamin D2. Vitamins D3 and D2 also can be supplemented in the ruminant diet by commercially available crystalline forms. Vitamin D3, arising from photochemical production in the skin, enters the extracellular fluid and becomes immediately available for further metabolism. However, when supplemented in the bovine diet, vitamin D metabolism actually begins in the rumen. Recent work in our laboratory showed that vitamin D2 and vitamin D3 are converted by microorganisms to trans-10-keto-19-nor-vitamin D (44). This metabolite may have a role in the in vitro deactivation of vitamins D2 and D3. Its physiologic importance and biochemical significance are not yet understood.

Once vitamin D (D2, D3, or both) enters the blood, it circulates at relatively low concentrations \((1\) to \(3\) ng/ml) in cows (29). This phenomenon is probably a result of its rapid accumulation in the liver. Once in the liver, it is converted to 25-hydroxyvitamin D \((25-\text{OHD})\) (14). This metabolite is the major circulating form of vitamin D under normal conditions (29). The 25-\text{OHD} is converted to several polar metabolites (Table 1). However, of all the vitamin D2 and D3 metabolites known, only
Figure 1. General scheme for calcium and phosphorus metabolism. Under normal conditions, flow to and from soft tissues is generally limited to phosphorus.

Table 1. Some of the identified vitamin D sterols.

<table>
<thead>
<tr>
<th>Vitamin D₂ forms</th>
<th>Vitamin D₃ forms</th>
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<tbody>
<tr>
<td>Vitamin D metabolites</td>
<td>Vitamin D metabolites</td>
</tr>
<tr>
<td>19-Nor-10-keto-vitamin D₂</td>
<td>19-Nor-10-keto-vitamin D₃</td>
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<tr>
<td>24-Hydroxyvitamin D₃</td>
<td>24-Hydroxyvitamin D₃</td>
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<tr>
<td>25-Hydroxyvitamin D₂</td>
<td>25-Hydroxyvitamin D₃</td>
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<tr>
<td>24,25-Dihydroxyvitamin D₂</td>
<td>23,25-Dihydroxyvitamin D₃</td>
</tr>
<tr>
<td>25,26-Dihydroxyvitamin D₂</td>
<td>23-Keto-25-Hydroxyvitamin D₃</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D₂</td>
<td>23,25,26-Trihydroxyvitamin D₃</td>
</tr>
<tr>
<td>24,25-Dihydroxyvitamin D₂</td>
<td>25-Hydroxyvitamin D₂-26,23 lactone</td>
</tr>
<tr>
<td>24-Keto-25-hydroxyvitamin D₃</td>
<td>24,25-Dihydroxyvitamin D₃</td>
</tr>
<tr>
<td>24-Keto-23,25-dihydroxyvitamin D₃</td>
<td>24-Keto-25-hydroxyvitamin D₃</td>
</tr>
<tr>
<td>25,26-Dihydroxyvitamin D₃</td>
<td>23-Keto-25-Hydroxyvitamin D₃</td>
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<tr>
<td>1,25-Dihydroxyvitamin D₃</td>
<td>23,25,26-Trihydroxyvitamin D₃</td>
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<td>1,24,25-Trihydroxyvitamin D₂</td>
<td>1,23,25-Trihydroxyvitamin D₃</td>
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<td>1,25,26-Trihydroxyvitamin D₂</td>
<td>23-Keto-25-dihydroxyvitamin D₃</td>
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<td>1,25-Dihydroxyvitamin D₂-26,23 lactone</td>
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<td>1,24,25-Trihydroxyvitamin D₃</td>
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<td>24-Keto-25-dihydroxyvitamin D₃</td>
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<td>24-Keto-1,23,25-Trihydroxyvitamin D₃</td>
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<td></td>
<td>1,25,26-Trihydroxyvitamin D₃</td>
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</table>
the function of 1,25-(OH)_2 D has been established. This metabolite (produced predominantly in the kidney), along with PTH, mediates blood Ca and P homeostasis. Figure 2 demonstrates the main factors regulating the kidney 1,25-(OH)_2 D biosynthesis. As shown, several factors may stimulate the 1α-hydroxylase; however, in the ruminant, the single most important influence appears to be PTH. Hove et al. (31) studied the influence of parathyroidectomy in lactating goats. Unlike rodents, the hypocalcemia (plasma Ca < 10 mg/dl) following parathyroidectomy in growing dairy heifers does not stimulate the formation of 1,25-(OH)_2 D. In addition, during PTH-induced hypercalcemia the 1α-hydroxylase and subsequently the plasma 1,25-(OH)_2 D concentrations were reduced. This result is in contrast to work in humans showing elevated 1,25-(OH)_2 D concentrations during acute PTH infusions (1) and during primary hyperparathyroidism (8) where plasma 1,25-(OH)_2 D,
PTH, and Ca were all elevated. Therefore, PTH, at least in young dairy heifers, is stimulatory to 1α-hydroxylase only during hypocalcemia and has no apparent effect on the 1α-hydroxylase during hypercalcemia. Conversely, the hypercalcemia produced secondary to the PTH infusions has a direct effect on inhibiting the kidney 1α-hydroxylase.

Hypophosphatemia can also have a direct effect on the kidney 1α-hydroxylase. In rodents fed low-P diets, kidney 1α-hydroxylase is stimulated. Recent work by Gray (21) has shown that this hypophosphatemic effect is mediated via the pituitary gland. They showed that hypophysectomy impaired the 1α-hydroxylase response in animals fed low dietary P but not animals fed dietary Ca.

There are many other vitamin D metabolites that circulate in the plasma of ruminants. Table 1 lists some of the vitamin D$_2$ and vitamin D$_3$ metabolites that have been identified. Although 1,25-(OH)$_2$D is proposed as the only active form of vitamin D, another metabolite produced mainly in the kidney, 24,25-dihydroxyvitamin D [24,25-(OH)$_2$D], may have a biological function. Plasma concentrations of this metabolite are low during vitamin D and Ca deficiency. Parathyroidectomy and vitamin D excess results in the elevation of 24,25-(OH)$_2$D in plasma (14). Parathyroid hormone, therefore, appears to inhibit the formation of 24,25-(OH)$_2$D from 25-OHD in favor of the formation of 1,25-(OH)$_2$D. Although the physiological significance of 24,25-(OH)$_2$D is still controversial, it appears to play a role in the formation of bone (5, 46). In addition, Somjen et al. (56) found receptors for 24,25-(OH)$_2$D in chondrocytes and proposed a possible mechanism in the normal formation of collagen. 24,25-Dihydroxyvitamin D has been proposed to be involved in a feedback loop resulting in the reduction of PTH secretion in dogs (9). This role for 24,25-(OH)$_2$D in other species has received little experimental support.

Recently, 24,25-(OH)$_2$D has been suggested to play a role in the onset of milk fever. Smith et al. (55) suggested a negative correlation between plasma 24,25-(OH)$_2$D and plasma Ca. Barton et al. (3) have also shown that injecting pharmacologic doses of 24,25-(OH)$_2$D to dairy cows around parturition resulted in an increased incidence of parturient paresis. Horst et al. (30), however, showed no significant difference in plasma 24,25-(OH)$_2$D concentration at parturition in animals developing parturient paresis compared with normal animals. Under physiological conditions, 24,25-(OH)$_2$D is unlikely to play any major role in the incidence of parturient paresis. However, when given in pharmacological doses that result in an elevation of plasma 24,25-(OH)$_2$D concentrations some 20 to 40-fold normal, such as those of Barton et al. (3), one may speculate that 24,25-(OH)$_2$D$_3$ is acting as an anti-1,25-(OH)$_2$D, preventing the biological action of 1,25-(OH)$_2$D at the intestine and bone.

Control of Calcium Absorption

When an animal is fed a diet containing less Ca than it requires, the proportion of dietary Ca actually absorbed is increased. Conversely, when an animal consumes more Ca than needed, the proportion of Ca absorbed decreases. The mechanism of this Ca adaptation is illustrated in Figure 3. As shown, the cascade of events ultimately leading to changes in Ca absorption efficiency are initiated by changes in plasma Ca but are ultimately under the control of the active metabolite of vitamin D$_3$, 1,25-(OH)$_2$D$_3$.

Although there is some evidence of Ca absorption occurring preduodenally (6), absorption of calcium from the gastrointestinal tract is controlled by a mechanism involving a feedback loop.

![Figure 3. Mechanism of adaptation to alterations in dietary calcium (Ca). The dashed line represents a response that occurs in rats but not in ruminants.](image-url)
tract occurs mainly in the upper small intestine. As described by Wasserman et al. (65), the transfer of Ca across the duodenal brush border occurs by facilitated transport and is initiated by 1,25-(OH)_2D. The 1,25-(OH)_2D mediates this response in a manner analogous to classical steroid action. The 1,25-(OH)_2D enters the enterocytes by diffusion and binds to its receptor in the cytosol. The 1,25-(OH)_2D receptor complex translocates to the chromatin fraction of the nucleus, and this nuclear receptor-hormone complex results in increased messenger ribonucleic acid synthesis and increased synthesis of specific proteins that control calcium transport. Transfer of Ca within the cytoplasmic compartment is also facilitated by 1,25-(OH)_2D and may involve the vitamin D-dependent, Ca-binding protein or encasement of Ca into vesicles. Several organelles, mitochondria, endoplasmic reticulum, and the Golgi sequester Ca and prevent buildup of Ca within the cytoplasm. Transport of Ca out of the cell is against a concentration gradient and is via a high affinity Ca-activated adenosine triphosphatase or Na+/Ca++ exchange.

Biological and Chemical Factors and Calcium Availability

As mentioned, the efficiency of Ca absorption from the intestine is influenced by several factors. Reducing dietary Ca (49) or increasing dietary acidity (38) results in more efficient Ca absorption. Age has a significant influence on the ability of the intestine to adapt to Ca stress. Aged animals are less able to increase absorption efficiency in response to dietary Ca stress when compared to young animals (26).

Dietary Ca-binding substances such as oxalate depress availability of Ca in non-ruminants as well as ruminants (64) and could account for the low availability of calcium in common feedstuffs such as alfalfa hay. Nucleic acids produced by bacteria, bacterial cell walls, dietary fat, large amounts of magnesium fluoride, and low dietary P have all been implicated in reduced availability of Ca for absorption (6).

Phosphorus Absorption

In contrast to Ca, dietary P is absorbed by ruminants in direct relation to P intake (10). However, unlike many species, the ruminant does not depend on the kidney as a major route of P excretion, its role being largely supplanted by the salivary glands. The large flow of saliva (25 to 190 L/d in cattle) contributes 30 to 40 g (70 to 80%) of the total endogenous P (62). The salivary P mixes with the dietary P before a portion of the total is absorbed during its passage through the small intestine. Thus, factors that influence the absorption of dietary P also affect the net loss of endogenous phosphate secreted from the salivary glands.

The P in saliva is almost all inorganic, and the ratio of the P content in parotid saliva to that in plasma is approximately 4.5 in cattle but higher (5 to 19) in sheep (11, 59). The total output of P in saliva is a function of many factors. When normal to high dietary P is consumed, P absorption is directly related to the amount of P in the diet and also directly related to the plasma P concentrations. There is, however, an inverse relationship to saliva flow (60). Factors that reduce the flow of saliva (fasting) can divert part of the endogenous P excretion from saliva to urine (59). The P concentration in saliva can also be influenced by PTH. Parathyroid hormone has been shown to increase P concentrations in saliva and thereby increase P secretion (62).

There is no doubt that, like Ca, the major site of P absorption is the small intestine (19). Until recently, it was thought that the amount of P absorbed from the intestine was regulated by the physicochemical characteristic of the P in the intestinal lumen. High dietary Ca, magnesium, aluminum, and iron have all been shown to form insoluble and, thus, unabsorbable complexes with P. However, we now know that, at least in monogastrics, P transport by the small intestine consists of both an active and passive process (66). The active process is separate and distinct from that associated with Ca transport and is readily saturable so that passive absorption predominates at higher luminal P concentrations. The active transport process is stimulated in animals fed low-P diets via the vitamin D pathway. As suggested in Figure 4, low plasma P will stimulate 1,25-(OH)_2D synthesis independent of Ca influences. The resulting increase in 1,25-(OH)_2D stimulates the intestine to absorb P more efficiently.

In ruminants, alteration in salivary P appears also to play a major role in P homeostasis. As
DECREASE IN P INTAKE
DECREASE IN P ABSORBED FROM GUT
DECREASED PLASMA
1, 25-(OH)2D3
DECREASE IN KIDNEY
1α-HYDROXYLASE
PITUITARY-MEDIATED INCREASE IN KIDNEY
1α-HYDROXYLASE
INCREASE IN PLASMA P
INCREASE IN P ABSORBED FROM GUT
INCREASE IN P INTAKE

Figure 4. Mechanism of adaptation to alterations in dietary phosphorus (P). (OH)2 = Dihydroxyvitamin.

stated earlier, P in saliva is directly correlated with plasma P. Injections of 1α-OHDD3 or intravenous infusion of P solution will increase plasma P as well as salivary P (10). In contrast, feeding low-P diets, which results in hypophosphatemia, leads to a decrease in salivary P (10). Reducing salivary P during P deficiency and increasing salivary P during P excess, therefore, represents an efficient method of P regulation unique to the ruminant.

Bone Metabolism of Calcium and Phosphorus

The skeleton contains 99% of the total Ca and 80% of the total P in the body. In ruminants, the amount of Ca and P deposited into bone is higher in younger animals than older (50). The amount of Ca deposited in bone reaches a maximum at about 1 yr of age and is reduced dramatically, leveling off at about 9 yr of age.

In young animals, bone formation occurs as a result of calcification of a specialized organic matrix. This process in long bones is known as endochondral bone formation. In this process, the epiphyseal plate cartilage elongates by proliferation of the resting chondrocytes. These cells mature into hypertrophic cartilage cells and at this stage have prepared their organic matrix for mineralization. Mineral is deposited on the matrix to give rise to endochondral calcification. In addition to this type of mineralization, there is also intramembranous bone formation, which does not involve chondroblast-mediated calcification. Instead, osteoblasts form a membrane of cell, which then elaborate organic matrix followed by the mineralization process. The shaping of bone follows a process involving a combination of endochondral and intramembranous formation.

Vitamin D plays an intimate role in the mineralization process. The major reason for failure of mineralization is an insufficient supply of Ca and P to the chondroblasts and osteoblasts that mediate formation of matrix. Whether there is an additional failure of mineralization process as a direct result of the absence of vitamin D metabolites is unclear. However, there is growing evidence that 24,25-(OH)2D or some metabolite of 25-OHD other than 1,25-(OH)2D plays a direct role in the mineralization process (5, 46).

Bone Ca and P mobilization in support of plasma Ca and P concentrations is under the influence of both 1,25-(OH)2D and PTH (Figure 2). Both 1,25-(OH)2D and PTH are needed for bone Ca resorption (14). During lactation, skeletal reserves of Ca and P are diminished but later replenished in late lactation and the ensuing dry period (6). During early lactation, the bone Ca and P resorptive response is somewhat refractory to the stimulus of PTH and 1,25-(OH)2D. As described by Ramberg et al. (49), early in lactation the animal depends mostly on Ca from the intestine. Bone resorption plays a very minor role until 1 to 2 wk postpartum. However, when cows are fed low-Ca diets prepartum, the bone contributes to the plasma Ca pool. This response is particularly useful in the prevention of milk fever (17) and is the basis of current dry cow management recommended by several universities.

Generally, bone deposition of Ca equals the amount of Ca resorbed. However, there are instances where either deposition or resorption occur at uneven rates. When bone deposition occurs more rapidly than resorption for a long time, the animals develop osteopetrosis. This disease can exist as a congenital defect or may be a result of dietary Ca excess (nutritional). Both congenital and nutritional osteopetrosis have been described in ruminants (35, 47). Nutritional osteopetrosis has been described only in bulls and was thought to result from feeding excess dietary Ca, which leads to hypercalcitonism. Because bulls rarely have a need to resorb bone (as opposed to lactating...
cows), bone formation predominates over resorption, resulting in osteopetrosis.

When bone resorption exceeds bone formation, a state of osteoporosis exists (15). This disease occurs primarily as a result of feeding for long periods a diet where Ca intake is less than Ca requirement, which causes Ca to be extracted from the bone. This disease rarely occurs in ruminants due to the high plane of nutrition practiced on today’s modern farms.

Feeding and Requirement

Several factors are known to influence availability and, therefore, requirements for Ca in feed (12). As stated earlier, feeding too little vitamin D can result in less Ca absorbed from the intestine. Hibbs and Conrad (23) studied the effects of various vitamin D supplementations on Ca digestibility. Dietary Ca was most efficiently digested when the cows received 40,000 IU of vitamin D/d. They also found low dietary P (3.5 mg/kg body weight) lowered Ca digestibility.

In addition to vitamin D and P, there are other dietary components that affect Ca metabolism. Feeding excess β-carotene decreases the utilization of vitamin D, and therefore Ca and P, and can result in rachitic bone lesions (20). Dietary protein has been reported to have no effect on Ca absorption in dairy cattle (61); however, Ca retention is decreased in pregnant sheep given a low-protein diet (57). Dietary Ca availability is also reduced by feeding large amounts of fat, possibly as a result of precipitation of Ca in the form of insoluble soaps (58).

Dietary P availability can similarly be affected by dietary constituents. Both low dietary protein and low energy reduce P availability in calves (36, 43). Contrary to monogastrics, ruminants can usually tolerate wider dietary Ca and P ratios without a noticeable reduction in P availability. However, there are times when they are detrimental. A large excess of Ca over P can reduce protein and carbohydrate digestibility (6). The ability to withstand wider Ca to P ratios by ruminants is thought to be a result of lower pH at the absorption site. Sheep have been shown to have a lower pH in the upper small intestine compared to monogastrics and, therefore, less Ca and P will be precipitated as insoluble tricalcium phosphate under the more acidic conditions (6).

There is also much variation in the availability of Ca from natural feedstuffs and dietary additives. Table 2 summarizes the comparative digestibility of Ca from various sources. Generally, Ca from inorganic sources has higher digestibility than that from organic sources such as hay. Also, as summarized, all sources of Ca are more efficiently utilized by younger animals — an expression of active bone growth (50).

Maintaining the Ca and P pool constant during lactation is a formidable challenge to dairy cows. During the course of a lactation (300 days), a cow producing 9,000 kg will secrete about 11.07 kg of Ca and about 8.56 kg of P into milk. If the Ca and P sources were 100% available, the cow would have to consume on an average about 37 g of Ca and about 29 g of P daily to meet her lactation needs. In lactating animals given a plentiful Ca and P intake, dietary sources of Ca are only about 38% available (33) and dietary P about 40 to 50% available (7). To meet her needs for lactation alone, a cow producing 9,000 kg of milk must therefore consume on an average 90 to 100 g Ca and 60 to 70 g P/d throughout lactation. An additional 25 to 30 g of Ca and 15 to 20 g of P must be supplied for maintenance. Using dry matter intake and milk production records reported by Moe (42) for high-producing (x = 9182 kg milk) cows and assuming 38% availability of dietary Ca, total dietary Ca can be calculated to maintain Ca balance throughout early and late lactation. Figure 5 contrasts the calculated Ca to that recommended by the NRC (45). Figure 6 expresses Ca as a percent of total diet. Clearly, animals fed Ca according to NRC recommendations may be consuming less than that required to maintain Ca balance in early lactation. Estimates from these data suggest that cows must be supplemented with 3.0 to 3.4 g Ca/kg milk, which represents a 10 to 20% increase in current supplement recommendations by NRC. This adjustment is largely a result of more accurate assessments of the biological availability of Ca under lactation conditions (23). Using data from balance studies, Ward et al. (63) estimated that to achieve Ca and P balance lactating cows must be supplemented at 5.0 and 2.4 g/kg milk, respectively. These data, in
TABLE 2. Biological availability of calcium from various sources for young and mature steers.¹

<table>
<thead>
<tr>
<th>Calcium source</th>
<th>True digestibility (%)</th>
<th>Biological availability (Mature %)</th>
<th>Biological availability (Young %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>40 51</td>
<td>100 100</td>
<td></td>
</tr>
<tr>
<td>Bonemeal (imported)</td>
<td>55 68</td>
<td>138 133</td>
<td></td>
</tr>
<tr>
<td>Calcium chloride</td>
<td>53 60</td>
<td>132 120</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate</td>
<td>50 64</td>
<td>125 126</td>
<td></td>
</tr>
<tr>
<td>Monocalcium phosphate</td>
<td>56 61</td>
<td>140 114</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate (A)</td>
<td>49 58</td>
<td>122 114</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate (B)</td>
<td>38 56</td>
<td>95 110</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate (C)</td>
<td>56 60</td>
<td>140 120</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate (D)</td>
<td>51 60</td>
<td>127 120</td>
<td></td>
</tr>
<tr>
<td>Dicalcium phosphate (E)</td>
<td>55 58</td>
<td>138 114</td>
<td></td>
</tr>
<tr>
<td>Defluorinated phosphate</td>
<td>40 55</td>
<td>100 108</td>
<td></td>
</tr>
<tr>
<td>Ground limestone</td>
<td>37 45</td>
<td>93 88</td>
<td></td>
</tr>
<tr>
<td>Alfalfa hay</td>
<td>31 41</td>
<td>78 80</td>
<td></td>
</tr>
<tr>
<td>Lespedeza hay</td>
<td>36 50</td>
<td>90 98</td>
<td></td>
</tr>
<tr>
<td>Orchardgrass hay</td>
<td>39 51</td>
<td>98 100</td>
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</tbody>
</table>

¹ Hansard et al. (22).

conjunction with recent availability estimates of dietary Ca and P (7, 23), suggest at least a 10 to 20% increase in both dietary Ca and P supplementation recommendations for lactation. Striving to maintain Ca and P balance during lactation is important, particularly in view of the current recommended practice of keeping dry cow dietary Ca and P at maintenance to minimize incidence of milk fever. These considerations reinforce the need for adequate Ca supplements in early lactation.

Milk Fever

One of the most common production diseases associated with parturition and early lactation is milk fever. Animals that develop milk fever are unable to meet their sudden demand for Ca, which is brought about by the sudden loss of this mineral from blood for formation of colostrum. Approximately 2.5 g of calcium are extracted from blood for each kilogram of colostrum produced. This is roughly equal to the total amount of calcium present in the blood at any given time. Therefore, a dairy cow producing 25 kg milk will have to replace her total blood Ca about every hour. The incidence of milk fever on an individual herd basis varies greatly but nationwide is approximately 5% of all milking cows. Recently, a comprehensive study by Curtis et al. (13) showed that the milk fever can reduce the productive life of a dairy cow 3 to 4 yr. In this study, which included 33 Holstein dairy herds, cows with milk fever were three to nine times more likely to contract other postpartum disorders such as dystocia, displaced abomasum, retained placenta, ketosis, and mastitis. In addition, cows contracting or suspected of contracting milk fever usually require constant watching for 2 to 3 d postpartum.

Several factors have been associated with a high incidence of milk fever. Studies have demonstrated that feeding high dietary Ca (100 g/d) prior to parturition results in a high incidence of the disease (32). Phosphorus supplementation to diets high in Ca may further potentiate the problem (4, 34). Under conditions of high dietary Ca and P and as the animal advances in age, plasma Ca is maintained almost solely by intestinal absorption with little or no contribution from bone stores (49). During conditions of acute Ca stress, such as the onset of lactation, cows become anorexic.
and plasma Ca begins to drop, resulting in an increase in plasma PTH and 1,25-(OH)\(_2\)D (28). These stimuli generally result in increased bone Ca resorption and increased intestinal Ca resorption. However, there is a subpopulation of cows (milk fever-prone) unable to respond to these stimuli. One of the hallmarks of a cow with milk fever is an acute inability to resorb Ca from bone. Microradiographic and histological evaluation of cortical and trabecular bone taken from milk fever-prone cows suggested this results from an impairment of osteoclast function. This was in contrast to the active osteoclast-mediated bone resorption occurring in normal animals or animals fed a low-Ca diet or large oral doses of vitamin D\(_2\) (52). The failure of osteoclastic response in milk fever is quite similar to that observed in congenital osteopetrosis, where bone resorption is also defective due to abnormal osteoclast function (33). Although still controversial, most evidence suggests that the formation of osteoclasts is affected by a cellular cascade involving the transformation of pluripotent hematopoietic stem cells to circulating monocytes to tissue macrophages with ultimate fusion to form multinucleated osteoclasts (39). Much evidence has accumulated in support of this theory, including the ability of monocytes and macrophages to resorb deactivated bone chips in vitro (34). Recently, Key et al. (34) demonstrated that in osteopetrosis, monocytes lose their ability to resorb bone in vitro. Supplementation with pharmacologic doses of 1,25-(OH)\(_2\)D improved the ability of the patients' monocytes to resorb bone in vitro. Moreover, the presence of 1,25-(OH)\(_2\)D enhances the maturation of monocytes to macrophages, which are thought to be direct precursors to osteoclasts (2). Milk fever, therefore, may represent an acute nutritional osteopetrosis similar to that in bulls fed high-Ca diets (35). The impaired osteoclast function may result from either a lack of or malfunction in precursor cells (monocytes). There are published reports of decreased monocyte numbers at parturition.
in cows (54), which, therefore, may ultimately translate into a decrease in osteoclast formation. It is unclear why monocyte numbers may decline at parturition. High concentrations of cortisol in plasma at parturition (27) may play a significant role since glucocorticoids are known immunosuppressants (51).

Milk Fever Prevention

The use of vitamin D and vitamin D metabolites has been very popular in attempts to prevent milk fever. These treatments include large oral doses of vitamin D_3 (24) and parenteral administration of the active vitamin D_3 analogues 25-OHD_3 (48), 1α-OHD_3 (40, 53), and 1,25-(OH)_2D_3 (16, 25). Each of these had been used with varying amounts of success. As described by Littledike and Horst (37), one potential problem with using these compounds is an inhibitory effect on kidney 1α-hydroxylase. In their study, many of the cows treated with vitamin D_3 or 1α-hydroxylated vitamin D_3 derivatives prepartum showed hypocalcemia and clinical signs of milk fever at 10 to 14 d postpartum. In control animals developing milk fever (Figure 7), plasma 1,25-(OH)_2D was inversely related to plasma Ca (r = –.82); however, in treated animals, plasma 1,25-(OH)_2D did not increase in response to hypocalcemia (r = .37). The animals in the latter group became dependent upon exogenous 1,25-(OH)_2D to reverse their hypocalcemia. This apparent drug dependency is a significant problem in the use of vitamin D analogues for milk fever prevention. We are attempting to overcome these problems in our laboratory by using slow-release implants to avoid acute drug withdrawal.

One of the most effective means to prevent milk fever is to avoid excessive dietary Ca in the prepartum diet (17). This approach takes advantage of the animal’s inherent Ca homeostatic mechanism and results in stimulating PTH and, ultimately, 1,25-(OH)_2D synthesis, which act to stimulate bone Ca resorption and intestinal Ca resorption. Data from Ramberg et al. (49) (Figure 8) show the relationship between dietary Ca, efficiency of dietary Ca absorption, and bone Ca resorption. As depicted when dietary Ca drops below 50 to 60 g/d the efficiency of absorption increases. When dietary Ca is as low as 10 to 15 g, the animals depend almost solely on bone Ca resorption to maintain the body Ca pool. Dietary Ca restriction is, however, difficult to implement under most management conditions because of the Ca content of many roughages. Careful selection of low Ca roughage and withdrawal of any Ca supplement, however, may achieve the desired effect.

CONCLUSIONS

Significant strides have been made in the last two decades to understand the regulation of Ca
and P homeostasis in mammals. Much of the basic information can be applied to ruminants. There are, however, specific areas where ruminants deviate from monogastrics, particularly with regard to the role of saliva in P homeostasis. The ruminant is the only animal that experiences crippling episodes of periparturient hypocalcemia or milk fever. Concerning milk fever, information is slowly accumulating as to the cellular lesions involved in disease, and hopefully an effective preventive program will eventually emerge. Finally, there is still a paucity of knowledge on availability of Ca and P in common ruminant feedstuffs and the effects of different physiological states on availability. However, recent estimations of dietary Ca availability during lactation lend support to increase the recommended Ca concentration in the diet of high-producing dairy cows from .6 to .75, particularly in early lactation.

REFERENCES

milk fever in dairy cows. IV. Prevention by short-
time prepartum feeding of massive doses of vitamin
25 Hoffsis, G. F., C. C. Capen, M. E. Packe, and A. W.
Norman. 1979. The use of 1,25-dihydroxychole-
calci ferol in the prevention of parturient hypo-
26 Horst, R. L., H. F. DeLuca, and N. A. Jorgensen.
1978. The effect of age on calcium absorption and
accumulation of 1,25-dihydroxyvitamin D₃ in
intestinal mucosa of rats. Metab. Bone Dis. Relat.
Res. 1:29.
plasma cortisol during induced and spontaneous
1978. Plasma 1,25-dihydroxyvitamin D and
parathyroid hormone levels in paretic dairy cows.
Am. J. Physiol. 235:E634.
of plasma concentrations of vitamin D and its
metabolite in young and aged domestic animals.
Comp. Biochem. Physiol. 73B:485.
30 Horst, R. L., R. M. Shepard, N. A. Jorgensen, and
H. F. DeLuca. 1979. The determination of vitamin
D metabolites in a single plasma sample. Changes
Biophys. 192:512.
31 Hove, K., R. L. Horst, E. T. Littledike, and D. C.
Beitz. 1984. Infusions of parathyroid hormone in
ruminants: Hypercalcemia and reduced plasma
Dairy Sci. 57:933.
33 Key, L. Y., D. Carnes, S. Cole, M. Holtrop, Z.
Bar-Savit, F. Shapiro, R. Arceci, J. Steinberg, C.
Gundberg, A. Kahn, S. Teitelbaum, and C. Anast.
1984. Treatment of congenital osteopetrosis with
34 Kichura, T. S., R. L. Horst, D. C. Beitz, and E. T.
Littledike. 1982. Relationships between prepartal
dietary calcium and phosphorus, vitamin D me-
tabolism and parturient paresis in dairy cows. J.
Nutr. 112:480.
35 Krook, L. L., L. Lutwak, K. McIntyre, P. A. Henriks-
36 Leibholtz, J. 1974. Flow of calcium and phos-
Res. 25:147.
37 Littledike, E. T., and R. L. Horst. 1982. Inap-
propriate plasma 1,25-(OH)₂D response to partu-
rient hypocalcemia in cows treated with vitamin
D₃, 1,25(OH)₂D₃ or 1,25,26(OH)₂D₃ prepartum.
Page 475 in Vitamin D, chemical, biochemical and
elemental endocrinology of metabolism. A. W.
Norman, K. Schaefer, D. V. Herrath, and H. G.
Grigoleit, ed. Walter de Gruyter, New York, NY.
38 Lomba, F., G. Chauvaux, E. Teller, R. Lengele, and
V. Bienfet. 1978. Calcium digestibility in cows as
influenced by excess of alkaline ions over stable
39 Louitit, J. F., and N. W. Nisbet. 1982. The origin
40 Marquardt, J. P., M. F. Holick, R. L. Horst, N. A.
Jorgensen, and H. F. DeLuca. 1974. Efficiency of
1α-hydroxyvitamin D₃ on prevention of parturient
1977. Effect of parity on dry matter intake at
42 Moe, P. W. 1965. Effects of level of intake on the
Cornell Univ., Ithaca, NY.
associative effect of feeds on the utilization of
nutrients from roughages. Ind. J. Dairy Sci. 20:5.
44 Napoli, J. L., J. L. Sommerfeldt, B. C. Pramanik,
R. Gardner, A. D. Sherry, J. J. Partridge, M. R.
Uskokovic, and R. L. Horst. 1983. 19-Nor-10-
keto-vitamin D derivatives: Unique metabolites of
vitamin D₃, vitamin D₂, and 25-hydroxyvitamin
45 National Research Council. 1978. Nutrient re-
quirements of dairy cattle. 6th ed. Washington,
DC.
46 Norman, A. W. 1980. 1,26-Dihydroxyvitamin D₃
and 24,25-dihydroxyvitamin D₃: Key components
of the vitamin D endocrine system. Contrib.
Nephrol. 18:1.
48 Olson, W. G., N. A. Jorgensen, L. H. Schultz, and
(25-OH-D₃). I. Treatment for parturient paresis. J.
Dairy Sci. 56:885.
49 Ramberg, C. F., E. K. Johnson, R. D. Fargo, and
D. S. Kronfeld. 1984. Calcium homeostasis in cows
with special reference to parturient hypocalcemia.
Am. J. Physiol. 246:R698.
50 Ramberg, C. F., D. S. Kronfeld, and G.D.A.
Wilson. 1975. Regulation of calcium metabolism in
cattle during growth, lactation, and change in diet.
Pages 231—242 in Digestion and metabolism in the
ruminant. I. W. McDonald and A.C.I. Warner, ed. 
51 Roth, J. A., and M. L. Kaeberle. 1982. Effect of
gluco corticoids on the bovine immune system. J.
52 Rowland, G. N., C. C. Capen, D. M. Young, and H.
E. Black. 1972. Micrographic evaluation of bone
from cows with experimental hypervitaminosis D
induced hypocalcemia, and naturally occurring
parturient paresis. Calcif. Tiss. Int. 34:564.
53 Sachs, M., A. Bar, R. Cohen, Y. Mazur, E. Mayer,
and S. Hurwitz. 1977. Use of 1α-hydroxycholecac-
ciferol in prevention of bovine parturient paresis.
paresis. VII. A study of the leukocytes of cows
55 Smith, P. N., M. Padilla, R. H. Wasserman, and F.
A. Kallfelz. 1982. Calcium and 24,25-dihydroxy-
vitamin D. Inverse relation in cows with parturient
paresis. Calcif. Tiss. Int. 34:564.
56 Somjen, D., G. J. Somjen, A. Harell, G. L. Mechanic,


