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PATHOPHYSIOLOGY OF CALCIUM AND PHOSPHORUS DISORDERS

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Adequate blood calcium (Ca) and phosphorus (P) concentrations are vital to normal function of animals. Mechanisms for maintaining blood Ca and P concentrations perform efficiently most of the time. Occasionally, these homeostatic mechanisms fail and metabolic diseases such as milk fever occur. An understanding of how and why these mechanisms fail may arise from a thorough understanding of how these mechanisms work under normal circumstances and an exploration of the possible sites for breakdown of homeostasis.

CALCIUM HOMEOSTASIS

Blood Ca in the adult cow is maintained at approximately 8.5 to 10 mg/dL, which means that there is approximately 3 g of Ca in the entire plasma pool of a 600-kg cow. The entire extracellular pool will have only 8 to 9 g of Ca. Many cows are producing colostrum and milk that contains 20 to 30 g of Ca each day. To prevent blood Ca from decreasing, which has a variety of severe consequences to life processes beyond paresis, the cow must replace Ca lost to milk by withdrawing Ca from bone or by increasing the efficiency of absorption of dietary Ca (Fig. 1). Although this is potentially damaging to bones and can lead to osteoporosis, the main objective—to maintain normocalcemia—can be achieved. Bone Ca mobilization is regulated by parathyroid hormone (PTH), which

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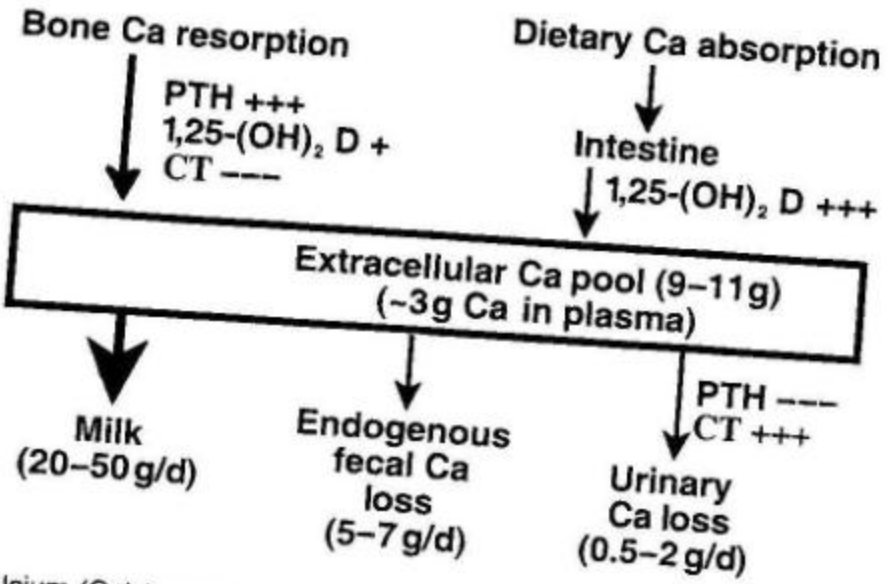

Figure 1. Calcium (Ca) homeostasis in a 500-kg cow. PTH = parathyroid hormone; CT = calcitonin; 1,25-$(OH)_2$ D = 1,25-dihydroxyvitamin D. + Stimulates movement of Ca in direction of arrow. − Inhibits movement of Ca in direction of arrow.

is produced whenever there is a decline in blood Ca. PTH also enhances renal tubular reabsorption of Ca; however, the total amount of Ca that can be recovered from urine is relatively small. A second hormone, 1,25-dihydroxyvitamin D, is required to stimulate the intestine to efficiently absorb dietary Ca. This hormone is made in the kidney from vitamin D in response to an increase in blood PTH. Put simply, hypocalcemia and milk fever occur when cattle do not remove enough Ca from their bones and the diet to replace Ca lost to milk. Why this might happen is explored in this article as each strategic point in Ca homeostasis is examined.

Factors Affecting Parathyroid Hormone Secretion

Hypomagnesemia

Parathyroid hormone secretion is normally increased greatly in response to even slight decreases in blood Ca concentration; however, hypomagnesemia can blunt this response.[56] This appears to be a factor in the development of some hypomagnesemic tetany syndromes of grazing beef and dairy cattle. Blood mineral profiles of lactating beef cows in one study demonstrated that plasma magnesium (Mg) concentrations declined slowly over several weeks after cows were placed on low-Mg, high-potassium pastures. Blood Mg concentrations declined to between 0.8 and 1.4 mg/dL; however, in animals with clinical disease (tetany), blood Ca had also fallen below 5 mg/dL. Tetany only occurred when plasma Ca concentrations declined in conjunction with plasma magnesium. Blood Ca concentration had remained within normal limits until the day the animals developed tetany. Plasma PTH concentrations

did not increase as a result of the decline in blood Ca concentration, and the authors concluded that hypomagnesemia had blocked PTH secretion, preventing the cows from maintaining normal Ca homeostasis.[42]

Low-Calcium Prepartal Diets

When cows are fed a diet that supplies less Ca than they require, the cows are in negative Ca balance. This causes a minor decline in blood Ca concentration, which stimulates PTH secretion, which in turn stimulates osteoclastic bone resorption and renal production of 1,25-dihydroxyvitamin D. This increases bone Ca efflux, and the intestine is ready to absorb Ca efficiently should it become available. At parturition, the lactational drain of Ca is more easily replaced because the cow's bone osteoclasts are already active and in high numbers, and, if supplied with Ca in the lactation ration, the previous stimulation of enterocytes by 1,25-dihydroxyvitamin D will allow efficient use of dietary Ca. Preparing the cow for a Ca demand before calving avoids the 2- to 3-day delay it can take to activate these mechanisms in the fresh cow and helps the cow avoid prolonged hypocalcemia.[23, 26, 28]

A truly low-Ca diet supplies less than 20 g of Ca per day. This is difficult to actually achieve on dairy farms, yet the strategy of reducing dietary Ca in prepartal rations often does reduce milk fever, even when the low-Ca diets are not truly low enough to stimulate PTH secretion. It may be that the switch from high-Ca feedstuffs (alfalfa, for example) to the low-Ca feedstuffs (corn silage, grass hays) actually reduces dietary cation (particularly potassium) content of the ration, as well as the dietary Ca content. When dietary Ca effects are separated from effects of strong dietary cations, it appears that Ca consumption has little influence on the incidence of milk fever when fed at levels above the requirement of the cow (more than 30 g of Ca/d).[5, 20] The concept of strong dietary cations, or the *dietary cation-anion difference* (DCAD), is discussed below.

Factors Affecting Parathyroid Hormone Action on Tissues

Acid–Base Status of the Animal and Acute Hypocalcemia

Metabolic alkalosis predisposes cows to milk fever and subclinical hypocalcemia.[12] Norwegian scientists,[13, 15] in a series of elegant studies, demonstrated that adding salts or acids containing specific anions to the diet of dairy cows prior to parturition effectively reduced the incidence of milk fever. Numerous studies since that time have demonstrated that adjustment of the relative dietary concentrations of certain cations and anions could help reduce the degree of hypocalcemia experienced by cows at parturition.[4, 6, 16, 22, 39, 48]

Two PTH-dependent functions, bone resorption and renal produc-

tion of 1,25-dihydroxyvitamin D, are enhanced in cows fed diets with added salts containing specific anions. This increases their resistance to milk fever and hypocalcemia.[6, 7, 16, 22, 65] In vitro studies demonstrate that simulating metabolic alkalosis in bone tissue culture systems reduces bone Ca resorption activity in response to PTH.[8, 45] As depicted in Figure 2, there is evidence to suggest that under normal conditions, when blood pH is about 7.35, PTH and its receptor, located on the surface of bone and renal tissue cells, interact in a tight "lock-and-key" fashion, allowing the PTH to adequately stimulate the target cell. Unfortunately, in cows fed a diet high in specific cations (see below), the blood pH may become alkaline, changing the conformational structure of the PTH receptor so that PTH and its receptor do not interact as efficiently. This reduces the cow's ability to respond to a Ca challenge.

Dietary Cation–Anion Difference and Acid–Base Status. In 1983, Stewart[62] proposed the strong ion difference theory of acid–base physiology. The basic tenet of this theory is that the number of moles of positively charged particles (cations) in any given solution (including body fluids) must equal the number of moles of negatively charged particles (anions) in the solution, and that the product of the concentration of hydrogen ions and hydroxyl ions is always equal to the dissociation constant of water, approximately 1×10^{-14}.

$$\text{no. of moles cations} = \text{no. of moles anions} \quad (1)$$

$$[H^+] \times [OH^-] = 1 \times 10^{-14} \quad (2)$$

Both equations must be satisfied simultaneously. Because pH is the negative log of the concentration of hydrogen ions, this essentially means that the pH of a solution is dependent on the difference between the

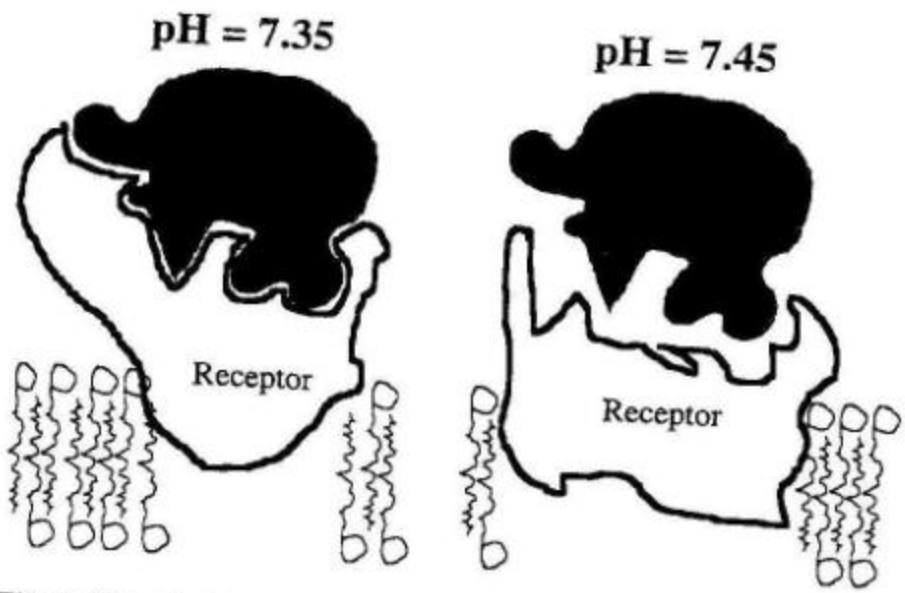

Figure 2. Effect of blood pH on the conformation of the parathyroid hormone (PTH) receptor located within the bilipid layer of the cell membrane of target bone and kidney cells.

number of negatively and positively charged particles in the solution. If positively charged particles are added to a solution such as the plasma, the number of H^+ cations will decrease and the number of OH^- anions will increase to maintain the electroneutrality of the solution (the solution becomes more alkaline). Conversely, adding anions to a solution causes an increase in H^+ and a decline in OH^- to maintain electroneutrality, and the pH decreases (the solution becomes more acidic). The primary cations and anions in the blood are described in the following paragraphs.

Bicarbonate Anions [HCO_3^-]. The blood HCO_3^- concentration is essentially determined by the concentration of CO_2 in the blood as predicted by the Henderson-Hasselbach equation, pH = pKa (6.1) + log HCO_3^- / H_2CO_3. Blood CO_2 concentration is under the control of the respiratory system and allows minute-by-minute fine tuning of blood pH. When respiratory function is depressed, CO_2 concentrations increase, increasing the carbonic acid concentration and causing blood pH to decline. Conversely, when respiratory rate is elevated (as occurs in heat stress), blood CO_2 and carbonic acid concentration decrease and pH increases.

Highly Dissociated Nonmetabolizable Anions and Cations. Highly dissociated nonmetabolizable ions are referred to as *strong ions.* The difference between the total number of strong cations and anions in the blood is referred to as the *strong ion difference.* Strong ions enter the blood from the digestive tract, making the strong ion difference of the diet the ultimate determinant of blood strong ion difference. Once absorbed, the concentration of strong ions in the blood is regulated by the kidneys. Adjustment of the strong ion difference of the blood is slower than respiratory control of blood pH but is capable of inducing much greater changes in blood pH.

In theory, all the cations and anions in the diet are capable of exerting an influence on the strong ion difference of the blood. The major cations present in feeds and the charge they carry are sodium (+1), potassium (+1), Ca (+2), and Mg (+2). The major anions found in feeds and their charges are chloride (−1), sulfate (−2), and phosphate (assumed to be −3). Cations or anions present in the diet will only alter the strong ion difference of the blood if they are absorbed into the blood. The trace elements present are absorbed in such small amounts that they are of negligible consequence to acid–base status. Organic acids, such as the volatile fatty acids, are generally absorbed in the undissociated form so that they carry both a positive and negative charge into the blood. They also are rapidly metabolized in the liver, so they have only a small effect on blood pH under most circumstances; however, in the case of lactic acidosis, the lactate anion can build up in the blood of the affected animal and cause severe metabolic acidosis.

The difference between the number of cation and anion particles absorbed from the diet determines the pH of the blood. The cation–anion difference of a diet is commonly described in terms of milliequivalents

per kilogram. This value is usually calculated from just sodium, potassium, chloride, and sulfate concentrations as follows:

$$DCAD = (Na^+ + K^+) - (Cl^- + S^{--})$$

In this equation, all concentrations are expressed as milliequivalents per kilogram (or alternatively as milliequivalents per 100 g). This equation is useful, although it must be kept in mind that Ca, Mg, and P absorbed from the diet also influence blood pH. We have evaluated the relative acidifying activity of various anionic salts by feeding them to dry cows and evaluating their ability to reduce urine pH (which reflects the changes in blood pH). These data lead us to believe the DCAD of a diet and its acidifying activity is more accurately described by the following equation: $(0.15\ Ca^{++} + 0.15\ Mg^{++} + Na^+ + K^+) - (Cl^- + 0.25\ S^{--} + 0.5\ P^{---})$. This equation suggests that the major dietary factors determining blood and urine pH are sodium (Na), potassium (K), and chlorine (Cl). It also suggests that sulfate is less acidifying than chloride, in general agreement with the findings of Oetzel et al.[49] Tucker et al[64] felt that sulfate was about 60% as acidifying as chloride. The particular coefficient is less important than the concept that chloride may be the better choice of acidifying agent. A complete equation should probably also include ammonium, because this cation seems to contribute to the cation content of the blood as well.[11]

Most nutritionists using the equation $DCAD = (Na^+ + K^+) - (Cl^- + S^{--})$ have a target DCAD for milk fever prevention of about −50 mEq/kg. Using the more physiologically relevant equation $(0.15\ Ca^{++} + 0.15\ Mg^{++} + Na^+ + K^+) - (Cl^- + 0.25\ S^{--} + 0.5\ P^{---})$, the target DCAD should be about +200 mEq/kg. Several of the variables in the above formulas are somewhat fixed. A strategy this author uses is to set dietary Ca at 1% to 1.2% and dietary P and Mg at 0.4% and to keep dietary sulfur above 0.25% (to ensure adequate substrate for rumen microbial amino acid synthesis) but below 0.4% (to avoid possible neurologic problems associated with sulfur toxicity[27]). The key to milk fever prevention is to keep Na and K as close to the requirement of the cow as possible (0.1% for Na and 1.0% for K). The key to reduction of hypocalcemia is to then add chloride to the ration to counteract the effects of even low levels of K on blood alkalinity. Further details on specific strategies for prevention of milk fever by dietary means are discussed in the article by Oetzel elsewhere in this issue.

These dietary suggestions are simply guidelines and are based on the setting of certain variables at constant values as outlined. Urine pH of the cows is a better gauge of the appropriate diet DCAD than any formula.[37] Urine pH on high strong-cation diets is generally above 8.2. Limiting dietary strong cations will reduce urine pH by only a small amount (down to 7.8). For optimal control of subclinical hypocalcemia and milk fever, the average pH of the urine of Holstein cows should be between 6.2 and 6.8. This essentially requires the addition of anionic salts to the ration. In Jerseys, the average urine pH of cows in the last 2 weeks of gestation has to be reduced to between 5.8 and 6.3 for effective

control of hypocalcemia. If the average urine pH is between 5.0 and 5.5, excessive anions have induced an uncompensated metabolic acidosis and the cows will suffer a decline in dry matter intake. Urine pH can be checked 48 or more hours after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. In cows offered feed twice per day, the timing of the urine collection does not seem critical. In cows fed fresh feed just once per day, the diurnal variation in urine pH can be a full pH unit. The best estimate of acid–base status appears to be from samples obtained 6 to 9 hours after fresh feed was offered.

The Concentration of Proteins. Proteins tend to be negatively charged and are considered anions. Their concentration in blood is generally dependent on liver function. Blood protein levels are fairly constant unless there are large changes in liver function or plasma volume.[11]

Magnesium Status

The integrity of the interaction between PTH and its receptor is vital to Ca homeostasis. Hypomagnesemia is also capable of interfering with the ability of PTH to act on its target tissues. When PTH binds its receptor, this normally initiates activation of adenylate cyclase, resulting in production of the second messenger, cyclic-AMP, or phospholipase C, resulting in production of additional cellular messengers, diacylglycerol and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C require Mg for full activity. In humans, it is well recognized that hypomagnesemia can cause hypocalcemia and that Mg therapy alone restores the serum Ca concentration to normal; Ca or vitamin D therapy is ineffective.[55]

Ordinarily, PTH increases renal tubular reabsorption of Mg, so the kidneys are excreting less of the excess dietary Mg absorbed. This causes blood Mg to be elevated in the typical milk fever cow[25]; however, if dietary Mg is insufficient or rumen absorption of Mg is impaired (see article by Martens and Schweigel elsewhere in this issue), there is no excess Mg to conserve and the plasma Mg concentration will fall below 1.85 mg/dL as a result of lactational drain of Mg. Sampling the blood of several cows within 12 hours after calving is an effective index of Mg status of the periparturient cows. If serum Mg concentration is not at least 2.0 mg/dL, it suggests inadequate dietary Mg absorption and that hypomagnesemia may be contributing to hypocalcemia in the herd. Mg content of the close-up dry cow ration should be between 0.35% and 0.4% to ensure adequate Mg absorption during this critical period.

Advancing Age

As animals age, the number of active bone cells is reduced. Heifers, who are still growing, rarely have problems with hypocalcemia. Lower

numbers of active osteoblasts means fewer cells to respond to PTH and mobilize bone Ca. In addition, as animals age, the number of receptors for PTH on target tissues declines.[29]

Hypocalcemia

Although hypocalcemia obviously is not the factor inducing hypocalcemia initially, it is possible that hypocalcemia—once it develops—reduces the ability of the animal to maintain Ca homeostasis.[53] Peptide hormones, such as PTH, often use changes in intracellular Ca concentration as a second messenger system to convey information from the cell membrane to the nucleus and cytoplasm of the cell. Hypocalemia may reduce target tissue intracellular Ca stores or reduce the influx of Ca into the cell in response to a Ca-regulating signal. Restoring blood Ca temporarily, as intravenous Ca treatment of the milk fever cow does, may be instrumental in allowing cells to regain sensitivity to PTH.

Factors Affecting Bone Mineral Resorption

Estrogen

Plasma estrogen concentrations (estradiol and estrone) rise dramatically in the final days prior to parturition.[61] Estrogens are potent inhibitors of bone resorption.[44] Several studies have suggested that cows with higher plasma estrogen concentrations at parturition were at greater risk of developing milk fever[31, 52]; however, several other studies have failed to make this link.[14, 58] It seems reasonable to believe the rise in estrogen is reducing the speed with which bone resorption can contribute to Ca homeostasis around parturition in all cows, but it does not appear to be the major factor inducing milk fever susceptibility in specific cows.

Calcitonin

Calcitonin, released by the thyroid C-cells in response to hypercalcemia, reduces Ca removal from bone and also increases urinary Ca excretion. Capen and Young[9] reported histologic evidence that calcitonin secretion was increased at calving in cows that developed milk fever. Assay of plasma calcitonin concentrations at parturition in normal and milk fever cows has failed to demonstrate a role for calcitonin in the development of hypocalcemia at calving.[31, 60]

Acid–Base Physiology

Bone acts as a major reservoir of buffer for acid–base control of body fluids. When animals are placed on acidifying diets, the blood pH decreases. To counteract the drop in blood pH, the bone releases cations (primarily Ca) into the blood to bring blood pH back toward normal.

Because the animals are in positive Ca balance at this time, the extra Ca entering the extracellular fluid Ca pool is excreted by the kidneys. Schonewille et al[59] have demonstrated that addition of anions to the diet of cows increased urinary Ca excretion from less than 0.1 g/d to 4.3 g/d before calving. When hypocalcemia was induced in these cows, the animals were able to reduce urine Ca excretion dramatically. These observations suggest that one of the mechanisms by which the anionic diets work is by inducing a low-grade Ca release from bone into the extracellular fluid Ca pool (4 to 5 g/d) prior to parturition. Upon parturition, the ensuing lactational drain of Ca is partially replaced by renal tubular resorption of this "bone" Ca. Although this 4 to 5 g of Ca resorbed from the urine appears to be a small amount relative to the total Ca lost to lactation, it should be kept in mind that the standard treatment for milk fever consists of 8 to 12 g of Ca administered intravenously, and this small amount effects a clinical cure in most cases.

Factors Affecting Renal Production of 1,25-Dihydroxyvitamin D

Horst et al[33] demonstrated that production of 1,25-dihydroxyvitamin D was similar in both milk fever and non–milk fever cows. In fact, peak plasma 1,25-dihydroxyvitamin D concentration was higher in milk fever cows than in non–milk fever cows; however, in reviewing plasma 1,25-dihydroxyvitamin D concentration profiles in cows that had not developed milk fever and those that developed a severe recurring milk fever with relapses to intravenous Ca treatment, it became clear that 1,25-dihydroxyvitamin D production was delayed and inadequate to increase intestinal Ca absorption in time to prevent hypocalcemia.[25] Full recovery from milk fever only occurred after the cow began synthesizing 1,25-dihydroxyvitamin D.

Dietary Cation–Anion Difference

Diets high in strong cations reduce renal synthesis of 1,25-dihydroxyvitamin D at the time of parturition in dairy cows.[16, 22, 51] The evidence suggests metabolic alkalosis reduces the sensitivity of the renal tissue to PTH (see previous section) so that the renal tissue fails to upregulate the 25-hydroxyvitamin D, 1α-hydroxylase enzyme needed to produce the hormone.

High Dietary Phosphorus

High blood P concentrations inhibit the activity of the renal 25-hydroxyvitamin D 1α-hydroxylase enzyme.[63] Kichura et al[41] fed Jersey cows diets supplying 10 g of P or 82 g of P per day. Cows fed the high-P diet had lower plasma 1,25-dihydroxyvitamin D concentrations before calving and more hypocalcemia than cows fed the low-P diets. Plasma

P concentration was greater than 6.0 mg/dL in the high-P diet cows. Barton et al[3] fed 21 cows a prepartal diet containing 120 g of Ca and 30, 60, or 90 g of P per day and determined that the incidence of milk fever was 0% (0/7), 29% (2/7), and 59% (4/7), respectively. Only those cows fed the highest dietary P level (90 g/d) had significantly elevated plasma P concentrations at calving.

As summarized by Jorgensen,[38] the incidence of milk fever increases when dietary P exceeds 90 g/d, and little negative effect of dietary P is seen when dietary P is less than 50 g/d. Feeding between 50 and 90 g of P per day is unnecessary and may contribute to hypocalcemia, but the data to prove this do not exist. Cows need 35 g of P or less each day.[47]

Vitamin D Deficiency

Vitamin D, supplied by irradiation of the skin or from the diet, is rapidly transported to and sequestered by the liver. Within the liver, vitamin D is converted to 25-hydroxyvitamin D and released into the blood. The production of 25-hydroxyvitamin D within the liver is dependent on the vitamin D supplied to the liver. Plasma 25-hydroxyvitamin D concentration is felt to be the best indicator of vitamin D status of an animal. Horst et al[35] have determined that plasma 25-hydroxyvitamin D concentrations below 5 ng/mL are indicative of vitamin D deficiency, and concentrations of 200 to 300 ng/mL indicate vitamin D toxicosis. Normal cows have plasma 25-hydroxyvitamin D concentrations between 20 and 50 ng/mL. A reasonable practice is to supplement the dry cow with 20,000 to 30,000 IU vitamin D per day.

Excessive Vitamin D

Earlier literature often recommended feeding or injecting massive doses (up to 10 million units of vitamin D) 10 days to 2 weeks prior to calving to prevent milk fever.[43] This will pharmacologically increase intestinal Ca absorption and can help prevent milk fever. Unfortunately, the dose of vitamin D that effectively prevents milk fever is very close to the level that causes irreversible metastatic calcification of soft tissues. Lower doses may actually induce milk fever because the high levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D induced by the treatment suppress PTH secretion and directly suppress renal synthesis of endogenous 1,25-dihydroxyvitamin D.[43] The animals become hypocalcemic when the exogenous source of vitamin D that had maintained elevated intestinal Ca absorption rates is removed from the body. In some cases, the renal tissues' ability to begin endogenous production of 1,25-dihydroxyvitamin D remains suppressed for a week after calving.[43] This problem of suppression of renal 1,25-dihydroxyvitamin D production can be minimized by slow withdrawal of the exogenous hormone over a period of days after calving.[19]

Treatment with 1,25-dihydroxyvitamin D and its analogues can be effective, but the effective dose is close to the toxic dose and problems

with timing of administration and withdrawal from treatment and expense have not made these treatments practical.[2, 21]

Dietary Calcium Absorption

Availability of Calcium from Feedstuffs

The amount of Ca that must be fed to meet the requirement for absorbed Ca is dependent on the availability of Ca in the diet and the efficiency of intestinal Ca absorption in the animal being fed. About one third to one fifth of Ca in plants is bound to oxalate, which is relatively unavailable to the ruminant.[67] Overall, the availability of Ca from forages like alfalfa may be only about 30%.[46, 66] Ca in mineral supplements is generally more available than Ca in forages and common feedstuffs,[30] with about 70% available for absorption.

This raises the possibility that two diets can be made, one based on alfalfa as a major source of Ca and the other using limestone as a source of Ca, that have the same amount of Ca in them; however, one diet meets the requirement of the cow's body for absorbable Ca, whereas the other does not. This can create problems for cows in midlactation. In midlactation, the cow is essentially totally dependent on intestinal Ca absorption to replenish blood Ca lost to lactation. If there is a sudden decrease in dietary Ca content or Ca availability from the diet, the animal may develop acute hypocalcemia. A sudden decrease in feed intake associated with estrus or inclement weather can also precipitate midlactation milk fevers. (Hypomagnesemia can also occur in midlactation to precipitate midlactation hypocalcemia.)

Age

With advancing age, there is a reduction in the number of receptors for 1,25-dihydroxyvitamin D in the intestine of cows.[34]

Ca-to-P Ratio in the Diet

The effect of the Ca-to-P ratio on absorption of Ca and P was once thought to be important, but many recent studies suggest that the Ca-P ratio is not critical unless the ratio is greater than 7 to 1 or less than 1 to 1.[38] Cows require grams of Ca and P, not ratios.

Dietary Fat

Some studies suggest that high-fat diets increase the dietary Ca requirement through the formation of Ca soaps[50]; however, the dairy industry has used Ca soaps of fatty acids as a source of energy for cows for a long time. Presumably, the Ca dissociates from the fatty acid within the small intestine to allow the fat to be absorbed. This should also

make the Ca free for absorption. No adjustment of dietary Ca for fat content of the diet should be required. This is not true for Mg. Because Mg absorption is highly dependent on rumen solubility, the formation of Mg–fatty acid soaps in the rumen could induce hypomagnesemia.

Lack of Production of 1,25-Dihydroxyvitamin D

This hormone is required for the active transport of Ca across the intestinal tract. It could be caused by vitamin D deficiency, which is rare, or renal inability to make 1,25-dihydroxyvitamin D, as discussed above.

Breed

The incidence of milk fever is higher in Jersey cows compared with Holstein cows. Although Jersey cow colostrum and milk Ca concentration tends to be higher than in Holsteins, this does not appear to be the only factor. Preliminary data from our laboratory suggest that intestines of Jersey cows possess about 15% fewer receptors for 1,25-dihydroxyvitamin D than do intestines of Holstein cows.[24]

The Effect of Colostrum Production

At parturition, colostrum production can impose a large drain on the plasma Ca pool. Milk Ca content is generally 1 to 1.1 g Ca/L. Colostrum Ca content ranges from 1.7 to 2.3 g/L.

Prepartum Milking

Removal of mammary secretions prior to calving can gradually induce lactation. In theory, the Ca demand would also slowly increase so that the animal would begin activating Ca homeostatic mechanisms prior to calving, which would reduce the risk of developing hypocalcemia at parturition. In practice, the response to prepartum milking has been mixed. If the animal was producing significant amounts of milk prior to calving (more than 8 kg/d), the prepartal milking was effective in preventing hypocalcemia. If little milk was produced during the last days of gestation, the degree of hypocalcemia was not improved.[40] The poor effectiveness and the lack of colostrum for feeding calves suggests that pursuing prepartal milking as a means of preventing hypocalcemia is not justified.

PHOSPHORUS HOMEOSTASIS

Phosphorus is a component of phospholipids, phosphoproteins, nucleic acids, and energy-transferring molecules such as ATP. P is an

essential component of the acid-base buffer system. It is second only to Ca as the major component of bone mineral.

Plasma inorganic P concentration is normally between 1.3 and 2.6 mmol/L or 4 and 8 mg/dL. About 1 to 2 g of P is present in the plasma inorganic P pool, and 4 to 7 g of P is normally present in the extracellular P pool of a 500-kg cow. Intracellular P concentration is about 25 mmol/L or 78 mg/dL, and total body intracellular P content is about 155 g, with 5 to 6 of those grams located within erythrocytes. Maintaining the extracellular P pool involves replacing P removed for bone and muscle growth, endogenous fecal loss, urinary P loss, and milk production with P absorbed from the diet or resorbed from bone[54] (Fig. 3). During late gestation, fetal skeletal development can withdraw up to 10 g of P per day from the maternal P pools.[36] About 0.3 g of P is incorporated into each kg of body tissue (muscle) gained during growth of the animal.[1] Production of milk removes about 1 g of P from the extracellular pool per kg of milk produced. Salivary secretions remove between 30 and 90 g of P from the extracellular P pool each day. Factors affecting salivary phosphate secretion include the time spent ruminating (chewing activity) and the PTH status of the animal. PTH stimulates parotid salivary P secretion[68] and can increase salivary phosphate concentrations two- to threefold. Salivary phosphate secretions help buffer the rumen and supply rumen microbes with a readily available source of P, which appears necessary for cellulose digestion. Most of the salivary phosphate secreted is recovered by intestinal absorption; however, even on low-P diets, a minimum of 5 g/d of secreted P is not recovered and is lost to feces. Urinary P loss is usually between 2 and 12 g/d. The bones of a 500-kg

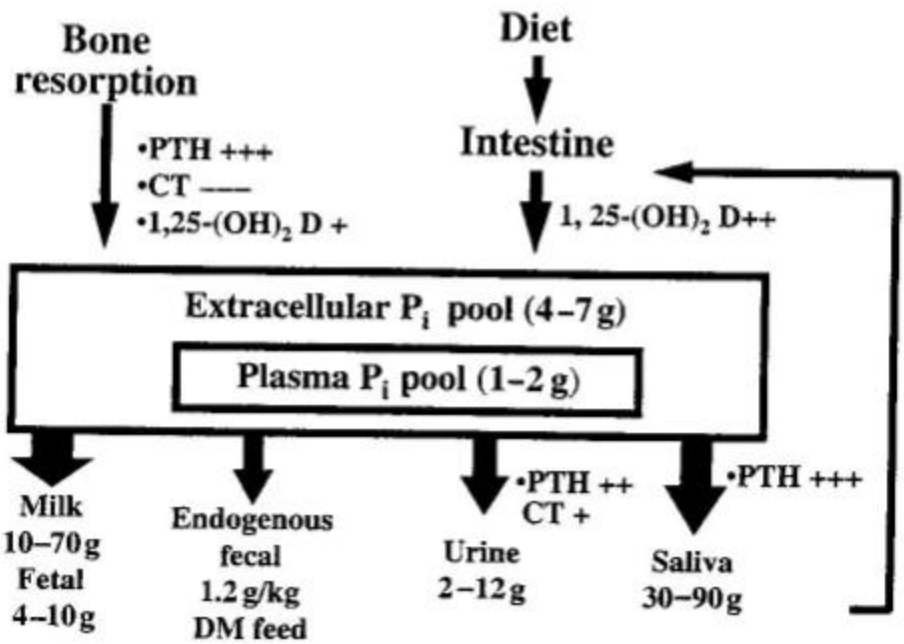

Figure 3. Phosphorus (P) homeostasis in a 500-kg cow. PTH = parathyroid hormone; CT = calcitonin; 1,25-$(OH)_2$ D = 1,25-dihydroxyvitamin D. + Stimulates movement of phosphate in direction of arrow. − Inhibits movement of phosphate in direction of arrow.

cow contain about 4 kg of P, some of which can be withdrawn and returned to the blood during osteoclastic resorption of bone.

Rumen microbes are able to digest phytic acid so that much of the phytate-bound P, the form of 35% to 70% of P in plants, is available for absorption in ruminants. Phosphorus is primarily absorbed in the small intestine via an active transport process that is responsive to 1,25-dihydroxyvitamin D. Intestinal P absorption efficiency can, in theory, be upregulated during periods of P deficiency as renal production of 1,25-dihydroxyvitamin D is directly stimulated by very low plasma P; however, the plasma P level must reach very low levels (less than 1 or 2 mg/dL) to actually stimulate increased renal production of 1,25-dihydroxyvitamin D. Plasma P concentrations are generally well correlated with dietary P absorption. Phosphorus absorbed in excess of needs is excreted in urine and saliva.

Factors Affecting Phosphorus Homeostasis

Parathyroid hormone, secreted during periods of Ca stress, increases renal and salivary excretion of P, which can be detrimental to maintenance of normal blood P concentrations. This is one reason that hypocalcemic animals tend to become hypophosphatemic. PTH could conceivably increase blood P concentration, because it stimulates bone mineral resorption; because it stimulates the kidney to produce 1,25-dihydroxyvitamin D, it can increase the efficiency of intestinal phosphate absorption. It must be remembered that PTH is secreted in response to hypocalcemia, not hypophosphatemia.

Problems Associated with Hypophosphatemia

Rickets and Osteomalacia

Rickets is a disease of young growing animals in which the cartilaginous matrix at the growth plate and the osteoid matrix formed during bone remodeling fail to mineralize. In adults (no active growth plates), the term *osteomalacia* is used to describe the failure of osteoid matrix to mineralize. Ca and P ions come together in a ratio of 10 Ca ions to six P ions at the point of mineralization of the bone cartilage or osteoid matrix. Failure to supply P in the diet will result in low plasma P concentrations that will not support this mineralization process, and the bone matrices will fail to mineralize.

Low plasma Ca concentrations (arising from vitamin D deficiency or severe Ca deficiency) can also result in failure to mineralize bone matrices. Bone ash is reduced, and the bones of young animals become "rubbery," bending without breaking. Joint surfaces are often eroded.

Chronic Hypophosphatemia

Animals fed diets containing less P than necessary to meet physiologic needs will suffer hypophosphatemia and all the physiologic consequences of failure to grow, inappetence, and unthriftiness. Milk production, but not P content, will decline. Impaired reproduction has often been attributed to P deficiency; however, in most cases in which cows develop P deficiency, the situation is complicated by concurrent energy deficiency, which was likely the direct cause of the reproductive failure.

Unfortunately, the belief that "marginal" dietary P contributes to reproductive inefficiency has been used as justification for feeding diets that are much higher in P than is required. Wu and Satter[69] present convincing evidence that high-producing cows perform well in terms of milk production and fertility when fed diets containing 0.37% to 0.40% P. A survey of nutritionists found that the average level of dietary P fed to commercial herds was about 0.52% dietary P for high-producing dairy cows.[57]

Acute Hypophosphatemia

Beef cows fed a diet marginal in P will have a chronic hypophosphatemia of 0.6 to 1.1 mmol/L, or 2 to 3.5 mg/dL. In late gestation, plasma P can decline precipitously as the growth of the fetus accelerates and removes substantial amounts of P from the maternal circulation. These animals often become recumbent and are unable to rise, although they appear fairly alert and will eat feed placed in front of them. Cows carrying twins are most often affected. Plasma P concentration in these recumbent animals is often less than 0.3 mmol/L, or 1 mg/dL. The disease is usually complicated by concurrent hypocalcemia, hypomagnesemia, and in some cases hypoglycemia.

At the onset of lactation, the production of colostrum and milk draws large amounts of P out of the extracellular P pools. This alone will often cause an acute decline in plasma P levels. In addition, if the animal is also developing hypocalcemia, PTH will be secreted in large amounts, which increases urinary and salivary loss of P. In dairy cows, plasma P concentrations routinely fall below the normal range at parturition, and in cows with milk fever, plasma P concentrations are often between 0.3 and 0.6 mmol/L, or 1 and 2 mg/dL. Plasma P concentrations usually increase rapidly following treatment of the hypocalcemic cow with intravenous Ca solutions. This rapid recovery is caused by reduction in PTH secretion, reducing urinary and salivary loss of P, and resumption of gastrointestinal motility accompanied by increased plasma concentrations of 1,25-dihydroxyvitamin D, which allows absorption of dietary P and reabsorption of salivary P secretions.[17]

Some animals developing acute hypophosphatemia do not recover normal plasma P concentration. This is sometimes the case in cows that are classified as "downer cows." This syndrome often begins as milk

fever, but unlike the typical milk fever cow, plasma P remains low (below 1 mg/dL) in some of these cows despite successful treatment of the hypocalcemia. Protracted hypophosphatemia in these cows appears to be an important factor in the inability of these animals to rise to their feet, but why plasma P remains low is unclear. In some cases the inability to absorb the salivary phosphate secondary to poor rumen motility may be a cause, but not in all cases. Excessive cortisol secretion could also drive blood P concentration down.[32] How this occurs is unknown. Treatment of cows with phosphate-containing solutions, but not phosphite-containing solutions, (orally or intravenously) can effect a recovery in some animals.[10, 18] The syndrome does not appear to be caused by low-P diets, because affected cows are often receiving diets containing 0.4% dietary P.

Postparturient Hemoglobinuria

Intravascular hemolysis, anemia, and hemoglobinuria is occasionally reported during the first 6 weeks of lactation. Many, but not all, cows developing this syndrome are hypophosphatemic. Severe hypophosphatemia is postulated to depress the ability of erythrocytes to produce ATP, because a key enzyme in glycolysis, glyceraldehyde-3-phosphate dehydrogenase, requires inorganic phosphate as a cofactor. Without sufficient ATP to power sodium pumps, the intracellular sodium concentration rises and the cells become more rigid and, as a result, rupture as they pass through the capillary beds. Hypophosphatemia alone is rarely sufficient cause for increased red blood cell fragility. Often, these cows are on diets that are also deficient in selenium, copper, and energy. Cows that have been treated for ketosis seem at greater risk of developing postparturient hemoglobinuria.

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