

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 then exploring the possible sites for breakdown of homeostasis.

Ca Homeostasis

Blood Ca in the adult cow is maintained around 8.5-10 mg / dl. This means there is about 3 g Ca in the entire plasma pool of a 600 kg cow. The entire extracellular pool will have only 8-9 g Ca. Many cows are producing colostrum and milk that contains 20 -30 g Ca each day. In order 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 efficient absorption of dietary Ca (Figure 1). While 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 is produced whenever there is a decline in blood Ca. Renal tubular reabsorption of Ca is also enhanced by PTH, however the total amount of Ca that can be recovered 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 within 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 below as each strategic point in Ca homeostasis is examined.

I. Factors affecting PTH secretion

A. Hypomagnesemia

PTH 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 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 only occurred when plasma Ca concentrations also declined. 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).

B. Low Ca 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 since 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 utilization of dietary Ca. Preparing the cow for a Ca demand prior to

calving avoids the 2-3 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 Ca/ 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. However it may be more likely that the switch from high Ca feedstuffs (alfalfa for example) to the “low Ca feedstuffs” (corn silage, grass hays) was actually reducing dietary cation (particularly potassium) content of the ration as well. When dietary Ca effects are separated from dietary DCAD effects it appears that dietary Ca has little influence on the incidence of milk fever when fed at levels above the requirement of the cow (>30 g Ca / day) (20) (5).

II. Factors affecting PTH action on tissues

A. 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 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 dietary cation-anion adjustment 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 production of 1,25-dihydroxyvitamin D, are enhanced in cows fed diets with added anions which 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 as well (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 high cation diet (see below) the blood pH may become more 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.

1. 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} .

$$1. \quad \# \text{ Moles cations} = \# \text{ Moles anions}$$

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

Both equations must be satisfied simultaneously. Since 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 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 :

a. 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, $\text{pH} = \text{pKa} (6.1) + \log \text{HCO}_3^- / \text{H}_2\text{CO}_3$. 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 concentration of HCO_3^- anion causing blood pH to decline. Conversely when respiratory rate is elevated (as occurs in heat stress) blood CO_2 declines, blood [HCO_3^-] declines and pH increases.

b. The concentration of non-metabolizable anions and cations.

The difference between the total number of non-metabolizable 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 cation-anion 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 and their charges found in feeds 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 within 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 mEq/kg of just sodium, potassium, chloride, and sulfate as follows:

Dietary Cation-Anion Difference (DCAD) = $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{S}^{--})$.

This equation is useful, although it must be kept in mind that Ca, Mg, and P absorbed from the diet will 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: $(0.15 \text{Ca}^{++} + 0.15 \text{Mg}^{++} + \text{Na}^+ + \text{K}^+) - (\text{Cl}^- + 0.25 \text{S}^{--} + 0.5 \text{P}^{--})$.

This equation suggests that the major dietary factors determining blood and urine pH are Na, K and 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 as this cation seems to contribute to the cation content of the blood as well (11).

Most nutritionists using the equation $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{S}^{--})$ have a target DCAD for milk fever prevention of about -50 mEq/kg. Using the more physiologically relevant equation,

$(0.15 \text{ Ca}^{++} + 0.15 \text{ Mg}^{++} + \text{Na}^+ + \text{K}^+) - (\text{Cl}^- + 0.25 \text{ S}^{--} + 0.5 \text{ P}^{---})$, 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 1-1.2% and dietary P and Mg at 0.4 %, and keep dietary sulfur above 0.25% (to ensure adequate substrate for rumen microbial amino acid synthesis) but below 0.4% (to avoid possible neurological problems associated with sulfur toxicity (27)). The key to milk fever prevention is to keep sodium and potassium as close to the requirement of the cow as you can (0.1% for Na and 1.0% for potassium). The key to reduction of hypocalcemia is to then add chloride to the ration to counteract the effects of even low levels of potassium on blood alkalinity. (Oetzel's chapter presents further details of methods to prevent hypocalcemia.)

These are simply guidelines and are based on the setting of certain parameters at constant values as outlined below. Urine pH of the cows will be the better gauge of the appropriate diet DCAD than any formula (37). Urine pH on high cation diets is generally above 8.2. Limiting dietary cations will reduce urine pH 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, which essentially requires addition of anions to the ration. In Jersey cows the average urine pH of the close-up cows 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 hrs 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 / day the timing of the urine collection does not seem critical. In cows fed fresh feed just once / 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 6-9 hrs after fresh feed was offered.

c. The concentration of proteins.

Proteins tend to be negatively charged and are considered as 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).

B. Mg status

As already discussed 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 the second messengers diacylglycerol and inositol 1,4,5-triphosphate. Both adenylate cyclase and phospholipase C require Mg for full activity. In man, it is well recognized that hypomagnesemia can cause hypocalcemia and that Mg therapy alone restores the serum Ca concentration to normal; Ca and/or vitamin D therapy are ineffective (55).

Ordinarily PTH will cause increased 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 Mg disorder chapter by H. Martens) 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 hrs 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.

C. 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).

D. Hypocalcemia

While 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 utilize changes in intracellular Ca concentration as a second messenger to convey information from the cell membrane to the nucleus and cytoplasm of the cell. Hypocalcemia 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.

III. Factors affecting bone mineral resorption

A. 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 (58) (14). 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.

B. 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) had 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).

C. Advancing age

Discussed above.

D. 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. Schoenwille et al (59) have demonstrated that addition of anions to the diet of cows increased urinary Ca excretion from less than 0.1 g / day g Ca / day to 4.3 g Ca / day prior to 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 (4-5 g/day) prior to parturition. Upon parturition the ensuing lactational drain of Ca is partially replaced by renal tubular resorption of this "bone" Ca. While this 4-5 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 8-12 g Ca administered intravenously and this small amount effects a clinical cure in most cases!

IV. 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.

A. Dietary cation-anion difference

Diets high in 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 section II-A) so that the renal tissue fails to upregulate the 25-hydroxyvitamin D, 1alpha -hydroxylase enzyme needed to produce the hormone.

B. High dietary P

High blood P concentrations inhibit the activity of the renal 25-hydroxyvitamin D 1a-hydroxylase enzyme (63). Kichura et al (41) fed Jersey cows diets supplying 10 g P or 82 g P / day. Cows fed the high P diet had lower plasma 1,25-dihydroxyvitamin D concentrations prior to 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 Ca and 30, 60, or 90 g P / day and determined the incidence of milk fever was 0/7 (0%), 2/7 (29%), and 4/7 (59%) 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 / day and little negative effect of dietary P is seen when dietary P is less than 50 g/day. Feeding between 50 and 90 g P / day is unnecessary and may contribute to hypocalcemia but the data to prove this do not exist. Cows need 35 g P or less each day (47).

C. 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 and released into the blood. The production of 25-hydroxyvitamin D within the liver is dependent on the vitamin D supplied to the liver. Thus plasma 25-hydroxyvitamin D concentration is felt to be the best indicator of vitamin D status of an animal. Horst et al, 1994 (35) have determined that plasma 25-hydroxyvitamin D concentration below 5 ng/ml are indicative of vitamin D deficiency and concentrations of 200 -300 ng/ml would 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 20-30,000 IU vitamin D / day.

D. Excessive Vitamin D

Earlier literature often recommended feeding or injecting massive doses (up to 10 million units of vitamin D) 10 days -2 weeks prior to calving to prevent milk fever [Hibbs, 1955 #60; (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-OH 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).

V. Dietary Ca absorption

A. Availability of Ca 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 1/3 to 1/5 of Ca within 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 within 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 utilizing 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 while the other does not. This can create problems for cows in mid lactation. In mid-lactation 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 mid-lactation milk fevers. (Hypomagnesemia can also occur in mid-lactation to precipitate mid-lactation hypocalcemia).

B. Age

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

C. Ca : P ratio in the diet

The effects of Ca:P ratio on absorption of Ca and P was once felt important but many recent studies suggest that Ca: P ratio is not critical, unless the ratio is greater than 7:1 or less than 1:1 [Miller, 1983 #517. Cows require grams of Ca and P , not ratios!

D. 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 utilized 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. Since Mg absorption is highly dependent on rumen solubility the formation of Mg-fatty acid soaps in the rumen could induce hypomagnesemia.

E. 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 due to vitamin D deficiency, which is rare, or renal inability to make 1,25-dihydroxyvitamin D , as discussed above.

F. Breed

The incidence of milk fever is higher in Jersey cows as opposed to Holstein cows. While 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 suggests that intestine of Jersey cows possesses about 15% fewer receptors for 1,25-dihydroxyvitamin D than do intestines of Holstein cows (24).

VI. The impact of colostrum production

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

A. Parturition 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 parturition milking has been mixed. If the animal was producing significant amounts of milk prior to calving (more than 8 kg / day) the parturition milking was effective in preventing hypocalcemia. If little milk is 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 pursuing parturition milking as a means of preventing hypocalcemia is not justified.

P Homeostasis

P 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 P concentration is normally between 1.3 and 2.6 mmol/L or 4 and 8 mg/dl. About 1-2 g P is present in the plasma inorganic P pool and 4-7 g 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 5-6 of those g 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) (Figure3). During late gestation fetal skeletal development can withdraw up to 10 g P / day from the maternal P pools (36). About 0.3 g P is incorporated into each kg of body tissue (muscle) gained during growth of the animal (1). Production of milk removes about 1 g P from the extracellular pool /kg of milk produced. Salivary secretions remove between 30 and 90 g 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 2-3 fold. 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/day of secreted P is not recovered and is lost to feces. Urinary P loss is usually between 2 and 12 g / day. Bones of a 500 kg 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 and 70% of P in plants, is available for absorption in ruminants. P 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. P absorbed in excess of needs is excreted in urine and saliva.

Factors affecting P homeostasis

PTH, 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 since it stimulates bone mineral resorption and because it stimulates the kidney to produce 1,25-dihydroxyvitamin D it can increase the efficiency of intestinal phosphate absorption. However, 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 remodelling 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 phosphate ions come together in a ratio of 10 Ca ions to 6 phosphate 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 which will not support this mineralization process and the bone matrices 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 suffer all the physiologic consequences of failure to grow, inappetance, and unthriftiness. Milk production, but not P content, will decline. Impaired reproduction has often been attributed to "P deficiency". However, in most cases where 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 contributed 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 0.37-0.40% 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 - 1.1 mmol/L or 2-3.5 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, though 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 due to 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 (orally or intravenously) can effect a recovery in some animals (10) (18). The syndrome does not appear to be caused by low P diets as affected cows are often receiving diets containing 0.4% dietary P.

Post-parturient 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 as 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, 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 post-parturient hemoglobinuria.

Synopsis

Ca and P homeostasis is challenged at parturition in cattle. The possible causes for a breakdown in Ca and P homeostasis that might be factors in the development of acute declines in plasma Ca and P concentrations are discussed, with major emphasis on the role of low Ca diets and dietary cation-anion difference in the etiology of milk fever. Disturbances in P metabolism can occur secondary to disturbances in Ca metabolism.

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Figure Legends

Figure 1. Calcium homeostasis in a 500 kg cow. PTH = parathyroid hormone, CT = calcitonin, 1,25-(OH)₂ D = 1,25-dihydroxyvitamin D.

+ = stimulates movement of calcium in direction of arrow

- = inhibits movement of calcium in direction of arrow

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

Figure 3. Phosphorus homeostasis in a 500 kg cow. PTH = parathyroid hormone, CT = calcitonin, $1,25\text{-(OH)}_2\text{D}$ = 1,25-dihydroxyvitamin D.
+ = stimulates movement of phosphate in direction of arrow
- = inhibits movement of phosphate in direction of arrow