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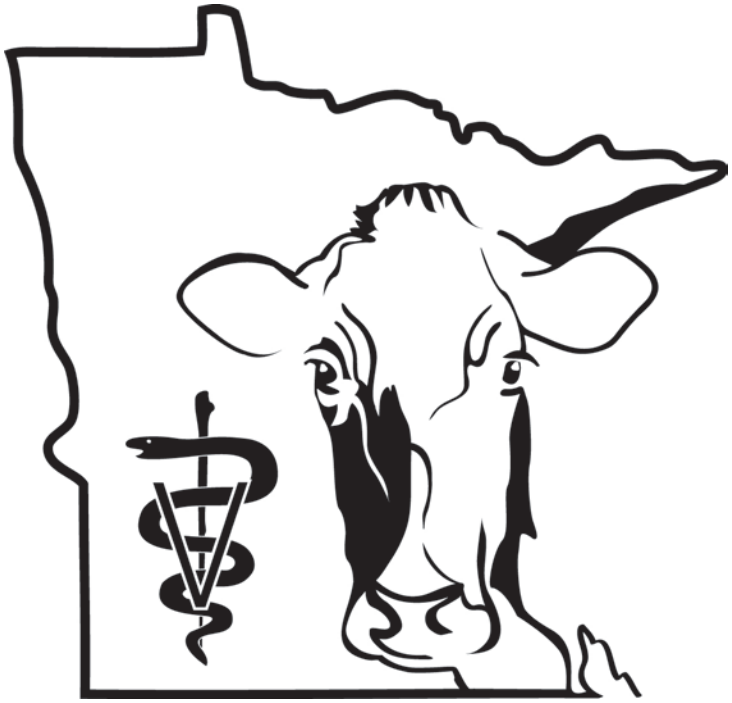

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CALCIUM METABOLISM, PATHOLOGY, TREATMENT REVIEW AND UPDATES TRANSITION COWS

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Dairy cows have an incredible demand for calcium (Ca) during early lactation. Cows may produce milk and colostrum that contain 20 to 50 g of Ca each day. Blood Ca concentration in the adult dairy cow is maintained at 8.5 to 10.4 mg/100ml (2.1 to 2.6 mmol/L), which means that the entire plasma pool of a 1300-lb cow is approximately 3.5 g of Ca (Goff, 2000). The entire extracellular pool will have only 9 to 10 g of Ca. Therefore, cows need to mobilize Ca from bone and/or increase the efficiency of absorption of dietary Ca in order to avoid a drastic reduction in blood Ca concentration during early lactation. Nearly all dairy cows will experience some level of subclinical hypocalcemia (< 7.5 mg/100 ml) within 24 hours of calving.

The hormone that regulates bone Ca mobilization is parathyroid hormone (PTH); its production is stimulated by a decline in blood Ca concentration. PTH also stimulates renal reabsorption of Ca and the production of 1,25-dihydroxyvitamin D by the kidney. This latter hormone stimulates the absorption of dietary Ca by the intestines. A summary of regulation of calcium homeostasis is depicted in Figure 1 (Goff, 2000).

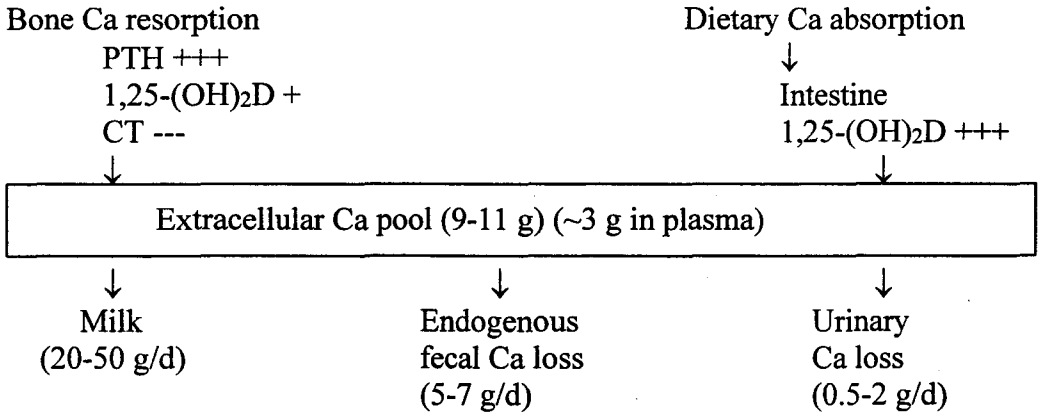

Figure 1. Calcium (Ca) homeostasis in an 1100-lb cow. PTH = parathyroid hormone; CT = calcitonin; 1,25-$(OH)_2D$ = 1,25 dihydroxyvitamin D; + Stimulates movement of Ca in direction of arrow; - Inhibits movement of Ca in direction of arrow.

Hypocalcemia and milk fever occur when the cow is unable to remove sufficient Ca from bones or the diet to replace Ca secreted in milk. Low blood Ca impairs abomasal contractions contributing to more abomasal displacement, prevents the teat sphincter from closing after milking contributing to increased incidence of mastitis, causes secretion of cortisol which impairs the immune system, can reduce feed intake resulting in higher risk for ketosis.

What are some of the factors affecting PTH activity? And what are some other aspects of Ca metabolism?

Secretion of PTH is stimulated by low blood Ca concentration. A factor than can stimulate PTH secretion is to feed a diet that supplies less calcium than required by the cow. This is difficult to do in practice, because it means to feed less than 15-20 g of Ca per day (Goff, 2000). Most rations provide more than that amount.

Scientists believe that Ca intake has little influence on the incidence of milk fever when fed at levels above the requirement of the cow (more than 30 g per day). Strong dietary cations, such as potassium, have a greater influence. It has been shown in various studies that a metabolic alkalosis makes cows more prone to develop milk fever and subclinical hypocalcemia. In cows fed diets high in some cations, blood pH may become alkaline and this changes the conformational structure of the PTH receptor, so that the hormone does not bind well with its receptor, therefore reducing the cow's ability to respond to a Ca deficiency. There is reduced bone resorption and reduced renal synthesis of 1,25-dihydroxyvitamin D.

The concept of dietary cation-anion difference (DCAD) has become popular in recent years. The major cation present in feeds and the charge they carry are sodium (+ 1), potassium (+ 1), Ca (+ 2), and Mg (+ 2). The major anions are chloride (- 1), sulfate (- 2), and phosphate (assumed to be - 3). The difference between the number of cation and anion particles absorbed from the diet determines pH of the blood. The DCAD is commonly described as $(Na^+ + K^+) - (Cl^- + S^{--})$ and expressed in milliequivalents per 100g or kilogram. A target DCAD to prevent milk fever is suggested to be about – 50 meq/kg. According to Goff (2000) a more physiological equation would be $(0.15\ Ca^{++} + 0.15\ Mg^{++} + Na^+ + K^+) - (Cl^- + 0.25\ S^{--} + 0.5\ P^{---})$, because it takes into account the fact that the major dietary factors are sodium (Na), potassium (K) and chloride (Cl), and that Ca, Mg, and P also influence pH, but to a lesser degree. The target DCAD using Goff's equation would be +200 meq/kg. Most nutritionists use the simpler, former equation. Dietary Ca should be set at 1 to 1.2% of diet dry matter, P and Mg at 0.4%, S above 0.25% but below 0.4%. Anionic salts can be added to the ration during the last two weeks of gestation. It is important to monitor urinary pH when feeding anionic salts. Average pH should be between 6.2 and 6.8 for Holsteins and 5.8 to 6.3 for Jerseys. If pH is lower than that excessive anions caused an uncompensated metabolic acidosis and cows will have reduced intakes. Prevention of milk fever by adding anionic salts to the diet will be mentioned again in the Transition Cow Nutrition Update article by Endres.

Schonewille et al. (1999) demonstrated in cows fed a diet rich in anions, the calcium intended for excretion with urine could be used to increase plasma calcium when the cow is under stress in early lactation. They used nonpregant, nonlactating cows as models and disodium-EDTA to bind plasma calcium. However, the amount of calcium derived from plasma, interstitial fluid, and the skeleton during EDTA infusion was quantitatively much more important to the supply of Ca than the reduction in Ca urine excretion.

Low blood magnesium can also reduce PTH activity because Mg is needed for full activity of two key enzymes – adenylate cyclase and phospholipase C – involved in the PTH response. It is suggested to sample the blood of several cows within 12 hours after parturition and if the Mg

concentration is below 2 mg/100 ml, Mg absorption is inadequate and hypomagnesemia might be one of the causes for hypocalcemia in the herd. It is recommended that the close-up dry cow ration contain 0.4% Mg.

Other factors that can negatively affect Ca metabolism/homeosthasis are advanced age, high plasma estrogen concentrations, increased calcitonin secretion at calving, high blood P concentrations (dietary P should be less than 50 g/d), vitamin D deficiency, low availability of Ca from certain feedstuffs, breed (Jerseys are more susceptible to milk fever compared with Holsteins).

Liesegang et al. (2000) demonstrated that cows with higher milk yield mobilize Ca more actively from bone than cows with lower milk yield and that all cows showed increased bone resorption around parturition. Their study compared cows with a mean standard milk yield of approximately 11,000 and 14,500 lbs. They measured hydroxyproline, deoxypyridinoline, pyridinoline and the carboxyterminal telopeptide of type I collagen (ICTP) as markers of bone resorption, and osteocalcin as bone formation marker in urine and blood samples. Samples were collected 14 d before, and 14 d, 1 mo, 1.5 mo, and monthly until 8 months after calving.

Is hypocalcemia related to milk yield?

Ostergaard and Larsen (2000) investigated the effect of total blood Ca concentration at calving on milk yield in dairy cows. Data was from 27 herds and 153 dairy cows from the same veterinary practice. Data included Ca concentration 12-h postpartum, monthly test-day milk yield until 300 DIM, calving date, parity, breed, and herd. Results of this study indicated that hypocalcemia (low blood Ca) at calving was not significantly related to milk yield. Other researchers, however, have reported a milk loss of 1.1 to 2.9 kg/d for a period of 4 to 6 weeks after calving in cows that contracted milk fever (Rajala-Schultz et al., 1999).

Effect of hypocalcemia on displaced abomasum and retained placenta

Delgado-Lecaroz et al. (1998) reported the occurrence of hypocalcemia in over two thirds of cows diagnosed with abomasal displacement or volvulus in 28 herds in New York. The average total serum Ca concentration was 0.8 mg/100 ml lower in cases than control cows. The difference tended to be larger for cows in third or greater lactation. Authors suggest that Ca administration at the time of abomasal displacement treatment may be beneficial. Other studies have shown an increased incidence of DA when blood Ca is low.

A significant association between parturient hypocalcemia, dystocia, and retained fetal membranes has been reported (Risco et al., 1999). Cows with hypocalcemia were 6.5 times more likely to have dystocia, 3.2 times more likely to have RFM and 3.4 times more likely to have a left-displaced abomasum. These conditions can negatively affect postpartum health and reproductive performance.

Effect of hypocalcemia on mastitis susceptibility

Calcium is needed for muscle contraction. Low blood Ca can reduce teat sphincter contraction, therefore the teat canal may remain open, resulting in more environmental pathogens entering the mammary gland. Goff and Kimura (2002) suggest that a depletion in intracellular Ca stores could contribute to a decline in immune function. However, they have not been able to demonstrate a correlation between the degree of hypocalcemia and the neutrophil/lymphocyte function in periparturient cows. Another way hypocalcemia can contribute to development of mastitis is by acting as a stressor to the cow, resulting in 5-6 fold increases in plasma cortisol, a immune suppressive agent.

Suggested treatments for hypocalcemia and milk fever

The fastest way to restore normal Ca concentration is the intravenous administration of Ca salts. Calcium gluconate has mostly replaced calcium chloride because it is less injurious when any subcutaneous leakage of solution occurs (Goff, 1999). Calcium chloride can cause localized sloughing of the skin. Boric acid is often combined with calcium gluconate resulting in calcium borogluconate, a more stable and soluble solution. In general calcium oxide is added to the solution to increase pH. These solutions normally supply 8.5 to 11.5 g Ca/100 ml. Other components may include sources of Mg, phosphite (not phosphate), and glucose. Goff (1999) suggests that the effective intravenous dose is just under 2 g Ca/100 kg of body weight. Calcium should be administered at a rate of 1 g /min. It is important to administer calcium slowly to avoid fatal arrhytmia of the heart. This will occur if plasma Ca becomes excessively high (more than 28 to 32 mg /100 ml). Plasma Ca remains normal for 4-6 hours after injection.

A continued decline in blood Ca concentration leads to clinical parturient paresis (milk fever). Symptoms include dullness, lack of coordination and recumbency. If untreated, milk fever can be fatal. The most common cause of downer (recumbent) cows is a complication of milk fever. Regardless of cause, a prolonged recumbency can lead to partial or total occlusion of the major blood vessels of the limb. This can result in necrosis of the major muscle groups of the hind limbs and irreversible muscle damage. There is a 4 to 6 hour window before ischemia of the muscles starts to occur (Coetzee, 2000). Downer cows need to be treated with an intravenous infusion of Ca salts. These solutions also contain a source of Mg and P as hypophosphite. Many drug treatments have been suggested for prevention of widespread muscle damage associated with downer cows. These include corticoids, stimulant tonics, vitamin E and selenium and non-steroid anti-inflammatory drugs, but there has been no consistent success. Cootzee (2000) suggests a 10 mg epidural dexamethasone injection has been of benefit in cases of obturator nerve paralysis detected at an early stage. Methylene blue given as intravenous injection appears to be helpful when widespread muscle hypoxia is suspected.

Treatment of hypocalcemia can also be done by subcutaneous Ca administration at a rate of 1 to 1.5 g Ca (usually 50-75 ml) per site. If greater amounts are injected, local tissue necrosis can occur. It is not recommended to use Ca chloride solutions. Solutions containing glucose can also be injurious to the tissue. In a severely hypocalcemic cow a subcutaneous injection might not result in a favorable clinical response. Care should be taken to avoid administering Ca

subcutaneously and then, because there was no visible response, inject Ca intravenously. A fatal hypercalcemia may occur.

Another method used to treat hypocalcemia is oral Ca administration. The passive diffusion of calcium across the intestinal mucosa is concentration dependent. The amount needed to make this happen is about 6 mmol/L. Most of the commercial supplements use calcium chloride (the most soluble salt) or calcium propionate as source of calcium. Calcium formate, calcium acetate, calcium gluconate and calcium lactate could also be used; calcium hydroxide, calcium oxide, and calcium carbonate are relatively insoluble and not suitable to treat hypocalcemia. Administration of 50 g Ca from calcium chloride as a drench in 250 ml of water is about the same as 4 g intravenously. Pastes and gels are also available, but a greater amount of calcium needs to be administered by gel or paste to get the same effect as an oral drench. The challenge is that hypocalcemic cows have poor swallowing and gag reflexes making them more susceptible to aspiration pneumonia. Another consideration relates to using calcium chloride or propionate – the former is slightly more effective and takes less volume, but it is irritating to mucous membranes. Calcium chloride oil emulsions have been used with success in Europe. It is suggested that the chloride in this preparation has an acidifying effect, causing a mild metabolic acidosis that activates Ca homeostasis mechanisms. If a herd was fed anionic salts in the prepartum diet, using calcium chloride could cause a severe metabolic acidosis with repeated treatments.

Melendez et al. (2000) conducted a field trial on a 3600 cow dairy farm in Florida and compared three treatments within 12 h after calving: no treatment; 51 g of calcium orally as calcium chloride; or 400 g of calcium propionate (100 g of Ca) plus 400 g of propylene glycol, orally. Cows in all treatments had received anionic salts in the close-up diet. Authors compared incidence of milk fever, retained fetal membranes, metritis, ketosis and displaced abomasum. They reported no differences among the three treatments, but suggested that sample size may have reduced the ability to detect differences.

Pehrson et al. (1998) compared the efficacy of calcium propionate with that of calcium chloride to prevent milk fever using 194 cows that had experienced milk fever during the previous calving. They used calcium propionate boluses and oily calcium chloride solution administered 24 h before expected calving, close to calving, and 12 and 24 h after calving. Authors concluded that calcium propionate had a comparable preventive effect to that of calcium chloride.

Aslam and Tucker (1998) infused 40 ml of either a 50% borogluconate solution containing 1.6 g of Ca or 40 ml of distilled, deionized water in the right forequarter of the udder of sixteen multiparous pregnant cows. They monitored changes in plasma Ca concentration every 10 minutes for the first hour after infusion and then hourly until the next milking. The infusion and sampling protocol was applied for three consecutive milkings (36 hours). Plasma Ca concentration of control cows decreased toward the end of each 12-h sampling interval but was more stable for cows infused with Ca. Authors suggested that infusing cows with Ca could reduce the incidence of metabolic disorders but there is the possibility of development of mastitis caused by the infusion procedure.

Is there an indicator for prognosis of clinical hypocalcemia?

Yamagishi et al. (2001) summarized research reports that indicate a high mortality rate in hypocalcemic cows showing lateral recumbency and disturbances of cardiac function, such as tachycardia, arrhythmia, and dyspnea. Focal acute myocardial necrosis was observed in hearts of cows that died with this condition. Clinical signs in these cows appeared to be more severe than milk fever cases where cows stand up after calcium treatment. Early on it is difficult to predict that hypocalcemic cows will die with acute myocardial lesions. Authors suggested that the concentration of atrial natriuretic peptide (ANP) might be a useful indicator of the prognosis of hypocalcemic cows with myocardial necrotic lesions. They compared two groups of cows and reported that ANP concentration in the plasma of the slaughtered group (cows that did not recover after Ca treatment) was 209.9 pg/ml and the ANP concentration in the plasma of the recovered group was 41.0 pg/ml, which is within the normal range (30 to 50 pg/ml).

A new theory on pathology and treatment of milk fever

A recent study by Sciorsci et al. (2001) has shed new light on the pathology of milk fever. Based on clinical signs of the disease – nervous disorders, anorexia, digestive atonia and meteorism, suppressed defecation, unconsciousness, cardiorespiratory difficulties, coma, tetany, and death – and the fact that endorphins increase at parturition, they suggested that endogenous opioid peptides (EOP) could be responsible for this pathology. In their study, cows with milk fever were administered the opiate antagonist, Naloxone (Nx) in Experiment 1 or Nx with Ca salts in Experiment 2 compared to traditional calcium pH or calcium borogluconate therapy. Naloxone alone induced the recovery of affected cows at a similar rate as traditional Ca treatments (Exp 1). In Experiment 2 a significantly higher ratio of cows recovered in less than 30 minutes in the group treated with Nx plus Ca salts than the group treated with Ca salts alone (90% vs 55%, respectively). The number of cows requiring repeated treatments was significantly reduced and no unrecovered cows were observed in the group treated with Nx plus Ca salts. The dose used in their study was 0.01 mg Nx/kg of BW, significantly less than the LD50 in rats and mice (640 mg/kg and 286 mg/kg, respectively). Their dose was comparable to the starting dose used in humans for opioid overdose therapy in addicts. The half-life of Nx is estimated as 15 to 20 minutes. This is the first full research paper reporting data on the interaction of calcium homeostasis and the opioidergic tone in the pathology of milk fever. Authors believe that EOP influence the balance between extracellular and intracellular calcium with a block of L-calcium gated channels. Finally, they conclude that Nx in association with Ca salts is an effective and safe therapy to treat cases of milk fever in dairy cows.

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Take-home messages

- Hypocalcemia can contribute to various periparturient disorders including displaced abomasum, ketosis, metritis, mastitis, and retained placenta.
- Hypomagnesemia can contribute to hypocalcemia.
- Blood alkalosis reduces PTH activity; feeding anionic salts can induce mild acidosis and help prevent hypocalcemia and milk fever.
- It is important to monitor average urine pH when using anionic salts – it should be 6.2 to 6.8 for Holsteins and 5.8 to 6.3 for Jerseys.
- Intravenous, subcutaneous and oral treatments of hypocalcemia last about 5-7 hours.
- It is not recommended to combine intravenous, subcutaneous and oral treatments because there is a risk of causing fatal hypercalcemia.
- Recent study suggests the involvement of endogenous opioid peptides in the pathology of milk fever.
- Based on that study, administration of Naloxone in association with Ca salts appears to be an effective therapy for milk fever.

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