Association between subclinical hypocalcemia and postpartum health disorders in dairy cattle

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Introduction

In dairy cattle, parturition and the onset of lactation lowers blood calcium concentrations (hypocalcemia) that can result in a clinical (milk fever) or subclinical condition. Cows with milk fever have paresis and require prompt calcium treatment. In contrast, in the sub-clinical form of hypocalcemia (SCH) the lower blood calcium concentration does result in paresis but does affect smooth muscle function (Huber et al., 1981) and immune function affecting health (Risco et al., 1984, 1994; Martinez- Patino et al., 2012). Many dairy producers have adopted the practice of feeding acidogenic diets prepartum that has contributed to a notable reduction in the incidence of milk fever with an average reported of 2.4 % (Reinhardt et al., 2011). However, despite the application of these diets, the prevalence of subclinical hypocalcemia (SCH) remains at 25 and 47% in primiparous and multiparous cows, respectively. Because of the higher prevalence and impact on health, there has been a resurgence in the interest to develop SCH prevention and therapeutic strategies. This paper discusses the association between hypocalcemia, postpartum health disorders and risk for metritis related to a reduction in immune function in dairy cattle. In addition, therapeutic considerations for SCH are discussed.

Association of calcium status to postpartum health disorders

Parturition and the onset of lactation predisposes cows to hypocalcemia characterized by a plasma calcium concentration < 8.5 mg/dl (Martinez et al., 2012; Chapinal et al., 2011). In cows with milk fever, decreased blood calcium concentration is accentuated and results in flaccid paralysis and eventually coma, if the animal is not treated. There is evidence that cows with milk fever, despite calcium treatment develop postpartum disorders. The association between milk fever and postpartum health disorders was evaluated in 33 Holstein dairy herds that involved 2,190 cows (Curtis et al, 1983). There were highly significant associations between milk fever and dystocia, retained fetal membranes (RFM), ketosis, and mastitis. The odds ratios for these associations were 6.5, 3.2, 8.9, and 8.1, respectively. Grohn et al. (1990), after evaluating the lactational and health records of over 61,000 dairy cows in Finland, found that milk fever was a significant risk factor for dystocia, RFM and clinical ketosis. The latter was associated with silent heats, cystic ovaries and infertility.

The effect of hypocalcemia on cow health goes beyond the clinical symptom of paresis. In a study involving sheep, Huber et al. (1980) demonstrated a true cause and effect relationship between hypocalcemia and normal smooth muscle contractility in the ruminant stomach. The major conclusions of this study were that: 1) ruminal contractions ceased long before signs of hypocalcemia were observed, 2) ruminal dysfunction may occur substantially before the clinical signs of hypocalcemia. In a study that evaluated the association between hypocalcemia and uterine prolapse, hypocalcemia without paresis was more common in cows affected with uterine prolapse when compared to cows without a prolapsed uterus (Risco et al., 1984) and cows with prolapsed uterus remained hypocalcemic during the first 7 days postpartum (Risco et al., 1994). Subclinical hypocalcemia has also been associated with digestive disorders, a higher risk of culling and lower fertility. Dairy cows that had abomasal displacement in an Iowa study had low blood calcium content preceding displacement (Hull et al., 1973). Similarly, cows with hypocalcemia without paresis where 4.8 times more likely to develop left displacement of the abomasum (Massey et al., 1993). Low serum calcium, <2.2 to 2.4 mmol/L from wk 1 through wk 3 postpartum were associated with reduced pregnancy at first AI (Chapinal et al, 2012).

Association between hypocalcemia and immune function

Hypocalcemia is a stressor and cortisol is a major contributor to immune suppression. Typically, cows have a 3-4 fold increase in plasma cortisol as a component of the parturition process. However, SCH cows can have a 5-7 fold increase in plasma cortisol on the day of parturition and cows with milk fever may exhibit plasma cortisol concentration that are 10-15 fold higher than pre-calving plasma cortisol concentration (Horst et al., 1982). Because immune suppression has been reported to begin 1-2 weeks prepartum (Kehrli et al., 1998[a,b]);

Horst et al., 1982) and the surge of cortisol is confined to the day of parturition, cortisol probably plays more of a contributing than a causal role in immune suppression.

The response of immune cells is complex. Generally, a compound such as a cytokine will bind to receptors on the immune cell surface, which then initiates an increase in intracellular ionized calcium (iCa) concentrations which act as a second messenger to alter intracellular metabolism, initiating the phagocytic and killing response of the cell. The source of calcium for this response is from the endoplasmic reticulum and mitochondria of the cell (Bréchard and Tschirhart, 2008). Immune cells of hypocalcemic cows have less cytosolic iCa available for activation and consequently, function is suppressed. As hypocalcemia develops in the extra cellular fluid, there is also a concomitant reduction of iCa2+ in the endoplasmic reticulum of the immune cells. Because of the insufficient stores of calcium in the endoplasmic reticulum, the response of immune cells to activating stimuli is blunted in cows with hypocalcemia (Kimura et al., 2006).

A series of experiments at the University of Florida (Martinez et al., 2012; 2014) were conducted to establish the associations between suboptimal blood calcium concentrations, immune function, physiological responses and uterine infections. Martinez-Patino et al (2012) evaluated the peripartal calcium concentration in cows at low or high risk (dystocia, retained placenta) of developing metritis during the first 12 days postpartum. On the basis of receiver operator characteristic curves, SCH was defined as a serum calcium concentration ≤ 8.59 mg/dL (< 2.124 mM) in at least 1 sample in the first 3 days postpartum. Also, cows with SCH (< 8.59 mg/dl) had elevated concentrations of NEFA and BHBA in serum during the first 12 days in milk, reduced neutrophil function and increased risk of developing metritis, compared to normocalcemic cows. This increased incidence of metritis in SCH cows was observed regardless of the risk group (high vs. low) for metritis at calving. Interestingly, the ability to maintain calcium concentration in blood during the first three days after calving was more important than the absolute calcium concentration; the greater the drop in calcium concentration in the first three days postpartum, the greater the probability of developing metritis later postpartum.

Martinez-Patino et al (2014) induced SCH (iCa < 1.00 mM) in healthy nonlactating dairy cows, simulating the loss of calcium of an early postpartum dairy cow. Cows with SCH had reduced rumen contractions, dry matter intake, elevated NEFA and glucose concentrations and decreased concentrations of insulin in plasma. The low calcium concentration likely compromised pancreatic release of insulin (Littledike et al., 1968) which may explain the increased concentrations of blood glucose and lipid mobilization based on elevation in plasma NEFA concentrations. Cows induced to develop SCH had a faster decline of cytosolic iCa in neutrophils after ionophore stimulation, which likely explains the compromised phagocytic and oxidative burst activities of these cells against pathogenic bacteria. Results from this study suggest that increased risk of diseases observed in cows that develop SCH in early lactation is, in part, caused by suppressed function of immune cells mediated by reduced cytosolic iCa concentrations.

Calcium therapeutic considerations

Calcium therapy by intravenous (IV) or oral route, is directed at maintaining normal plasma calcium concentrations. In cases of milk fever immediate parenteral IV calcium therapy (8.5 to 11.5 g calcium) is warranted. However, oral calcium supplementation is recommended for cows with undetected SCH or those in stage 1 milk fever (Oetzel, 2011). Total serum calcium dynamics were evaluated after prophylactic treatment of SCH after parturition in 33 multiparous Jersey x Holstein crossbreed cows (Blanc et al 2014). Compared to oral calcium treatment, IV calcium administration resulted in total serum calcium concentrations that reached hypercalcemic levels (11.4 mg/dL) that peaked 1 hour after treatment and declined to hypocalcemic levels by 24 hours after treatment. The short duration of hypercalcemia observed after IV Ca supplementation may have impaired the ability of the animal to maintain calcium homeostasis. According to Goff (1999), hypercalcemia causes a decrease in blood parathyroid hormone levels and an increase in thyrocalcitonin release, which decreases renal and bone Ca reabsorption, decreases calcitrol conversion to 1, 25-dihydroxyvitamin D, increases aciduria, and depletes blood of cations. Whether or not the hypocalcemia that resulted from IV Ca treatment in the Blanc et al. (2014) study affected health and productivity was not reported.

Oral supplementation of soluble calcium salts are commercially available that are suitable to treat SCH cases and prevent relapses in milk fever cases after IV calcium treatment. Oral calcium compounds have been

developed to take advantage of passive diffusion of ionized calcium across cellular tight junctions in the rumen and intestines (Goff & Horst, 1993, 1994).

The effect of oral calcium supplementation in early postpartum dairy cows has been studied but results have been inconsistent. A field study evaluated the effects of oral drenching with additional energy or energy plus calcium on blood parameters and performance of postpartum dairy cows (Stokes et al., 2001). Treatments were 9.5L water (control), 9.5L water plus 300mL (310g) propylene glycol (PG), or 9.5L water plus 0.68kg calcium propionate (CP). Cows received the assigned drench within 4 h of calving and again 24 h after calving. Drenching with PG or CP had no effect on plasma concentrations of calcium and glucose, or milk yield compared with control cows. However, cows receiving either PG or CP at calving had a significantly lower incidence of metritis compared with control animals. Averaged across all trial periods, animals receiving PG had 3.1 kg/d greater milk production than those receiving the control. Another study performed by Melendez et al. (2003) that evaluated the effect of no oral calcium treatment, 60g of calcium as CaCl2 , 110g of calcium as calcium propionate in combination with 400g of propylene glycol on calving-related disorders, fertility and milk yield. The results showed no effect of treatment on incidence of diseases, milk yield or reproductive performance. In contrast, a study performed by Oetzel (1996) evaluated the effects of supplementation with oral Ca on incidence of hypocalcemia and early postpartum diseases. The treatments consisted of no oral calcium, or 54g of oral calcium as CaCl2 gel containing 1.5g of Mg and 8.2g of P to cows 12h before expected calving, immediately after calving, at 12 and at 24h after calving. Treatment with 54g of oral calcium increased serum calcium concentrations by 0.72 mg/dL during the first 2 days postpartum, and reduced the incidence of clinical and subclinical hypocalcemia, but no effect of treatment was found for retained fetal membranes but it did reduce the incidence of displaced abomasum. A study by Oetzel and Miller (2012) evaluated the effect of oral administration of two doses of 43g of Ca as CaCl2 and CaSO4, after calving and the second one 8 to 35 h later, on health and milk yield. The authors observed no differences in serum calcium concentrations, but a reduced incidence of health events in the first 30 days postpartum in cows considered lame. In addition, cows with a previous lactation mature equivalent greater than 105% of herd average produced 2.9 kg more milk in the first test postpartum when treated with calcium compared with untreated controls in the same milk category.

Studies have been conducted to evaluate the benefits of different doses and duration of calcium supplementation on cohort of dairy cows with different susceptibility to hypocalcemia. Oral calcium supplementation with 43g or 86g calcium as CaCl2 and CaSO4 (Bovikalc bolus, Boehringer Ingelheim, St. Joseph, MO) increased iCa concentrations in blood, but the increase in iCa and total calcium lasted fewer than 2 hours with 43g and fewer than 8 hours with 86g (Martinez-Patino et al., 2016[a]). Supplementing oral calcium at these doses reduced the incidence and prevalence of SCH and these reductions were greater when supplementation was extended to 4 days in milk. Interestingly, despite the reduction in the incidence of SCH, oral calcium supplementation increased the incidence of metritis in primiparous cows considered to be at low risk of metritis. Conversely, multiparous cows supplemented with oral calcium had reduced incidence of diseases other than metritis and ketosis. Another study that involved 450 Holstein cows, evaluated the effects of oral calcium supplementation on milk yield, body condition, pregnancy per AI, and days to pregnancy in Holstein cows considered to be of low or high risk of developing metritis (Martinez-Patino et al., 2016 [b]). Cows were randomly assigned to control (no calcium supplementation), 86g of calcium ((Bovikalc bolus, Boehringer Ingelheim, St. Joseph, MO) at calving and 1 day postpartum, or 86g of Ca at calving and 1 day postpartum followed by 43g/d on d 2 to 4 postpartum. Supplementation with oral Ca had no effect on the change of body condition in the first 32 days postpartum. Interactions with risk of metritis and production potential in multiparous cows were observed in the first 30 days of lactation. Within multiparous cows, those with greater potential for production benefited from supplemental calcium, whereas cows of less production potential had depressed milk yield when they received oral calcium. Supplementing primiparous cows with oral calcium lowered pregnancy per AI and rate of pregnancy. In contrast, the same strategy to multiparous cows improved pregnancy per AI and increased pregnancy rate. Based on these results, the authors suggest that oral calcium supplementation at calving should be avoided in primiparous cows and target only populations at high risk of developing hypocalcemia such as multiparous cows.

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