Impact of Subclinical Hypocalcemia on Dairy Cattle

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Summary

The objective of this proceedings paper is to summarize some current knowledge on subclinical hypocalcemia (**SCH**) and highlight the importance of calcium (**Ca**) homeostasis and homeorrhesis at initiation of lactation. There is vast literature on the associations of suboptimal blood Ca concentration in fresh cows with an impaired immune system, as well as its connections with energy metabolism, early lactation diseases, culling, milk production, and reproductive performance; we will touch on the various studies done and emphasize on some common findings. However, as most studies follow an observational study design, causation cannot be established though indicate a characteristic (i.e., suboptimal blood Ca concentration) that is symptomatic of a problem. Also, the literature is often inconsistent when evaluating the impact of SCH with postpartum health and lactation performance; this is most likely due to the temporal associations of Ca concentration in early postpartum and the parity dependence with the outcomes analyzed.

Introduction

The period surrounding parturition is a challenging time in the life cycle of a dairy cow. Abrupt changes in diet, management, and cow physiology occur altogether in this period. Importantly, the increased demand for Ca at the time around calving must be readily met or a clinical disease state (milk fever) occurs. With the advance in knowledge of risk factors for clinical hypocalcemia and nutritional products available to feed the close-up dry cow to modulate Ca homeostatic mechanisms, nutritionists and veterinarians are better armed with tools to best prepare the dairy cow to the increased Ca requirements at colostrogenesis and lactogenesis. However, a subclinical disorder still seems to prevent optimal cow performance.

Calcium plays very important physiological and biochemical functions in the body, such as acting in cell signaling as a secondary messenger, being an enzyme co-factor, actively acting in muscle contraction, growth, gluconeogenesis, glycolysis, membrane stabilization, and cellular proliferation (Berridge, 1993; Jaiswal, 2001). Calcium homeostasis is regulated by 3 major target organs: bone (Ca resorption), gastrointestinal tract (Ca absorption), and the kidneys (Ca reabsorption).

Calcium Homeostasis

Calcium homeostasis is a complex multistep process, and there are 3 main hormones responsible for Ca regulation: parathyroid hormone (**PTH**), the active form of vitamin D (calcitriol), and calcitonin (the last not being discussed in this paper). These hormones

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are responsible for mediating the increase or decrease in blood Ca concentration by acting on the GI tract, bones, and kidneys. Calcium-sensing receptors (G protein-coupled receptors located on the cell membrane of the parathryoid chief cells) are responsible for sensing changes in ionic Ca concentration and either increase (during hypocalcemia) or decrease (during hypercalcemia) the release of PTH. During low levels of Ca, PTH is released within a few seconds through exocytosis and has a half-life of only a few minutes (Mannstadt et al.,1999), where it will reach 2 organ targets via bloodstream: the kidneys and bones. After PTH binding to its receptor, activation of adenylyl cyclase must occur. In this process, Mg is a co-factor required for enzyme activity (Rude, 1998; Quitterer et al., 2001). Rude (1998) demonstrated in humans that hypomagnesemia can directly affect PTH organ activity and impair Ca homeostasis.

Mg feeding rates and sources can have an impact in postpartum Ca balance. Meta-analyses work shed evidence that higher Mg feeding rates (an increase from 0.3% to 0.4% on a DM basis) were necessary to reduce the risk of clinical hypocalcemia (Lean et al., 2006). It has been speculated that higher Mg feeding rates could take full advantage of Mg passive absorption in the rumen (Goff, 2008). If using higher prepartum Mg feeding rates (e.g., 0.45% DM), adoption of an ordinary source or a more bioavailable Mg does not seem to affect prepartum plasma Mg concentrations (Leno et al., 2017).

Vitamin D is another key component in the maintenance of Ca balance. In the plasma of cattle, vitamin D_3 (25-hdroxyvitamin D_3 or cholecalciferol) is more abundant than D_2 and thought to be of greater relevance (Horst and Littledike, 1982). Cholecalciferol is majorly supplied through the diet, though it is also synthesized in the skin from 7-dehydrocholesterol in a conversion catalyzed by ultraviolet irradiation. Briefly, there are 2 hydroxylation processes prior to conversion to the metabolically active compound (calcitriol; 1,25$(OH)_2D_3$). The first hydroxylation process occurs in the liver (enzyme: calciferol-25-hydroxylase), while the second occurs in the kidney (enzyme: 25-hydroxycholecalciferol-1-α-hydroxylase; stimulus: PTH; site: mitochondria of renal epithelium cells in the proximal convoluted tubes). As a result, calcitriol stimulates activation of vitamin D receptors in the kidney and bones (increase in Ca reabsorption and resorption, respectively) and intestines (increase in Ca absorption).

It is more plausible to think that vitamin D acts in a homeorrhetic manner during lactation as production of calcitriol is dependent on PTH (homeostatic response). For instance, 25-hydroxycholecalciferol-1-α-hydroxylase activity is ablated in lactating rats that are parathyroidectomized. Moreover, the activity of vitamin D has shown to be time-dependent. In a cell culture line of pig kidney incubated with an active vitamin D analog, the vitamin D receptor only reached its peak up-regulation after 16 to 20 hr (Costa et al., 1985). Administration of active vitamin D analogues have been shown to have a peak effect on blood Ca levels after 2 to 3 days following administration in cattle (Vieira-Neto et al., 2017).

In addition to PTH, parathyroid hormone-related protein (**PTHrP**) expressed during lactation can support Ca balance. PTHrP is secreted by the mammary gland and perform similar actions in the kidney and bones when compared to PTH (Horseman and Hernandez, 2014).

Subclinical Hypocalcemia

For definition purposes, one should classify SCH as low serum or plasma Ca concentrations (without visible signs) that are associated with periparturient health disorders, and/or poorer production and reproduction outcomes. The complicating factor is that there is no consensus in the literature as to how (i.e., what cut-point to use) and when to classify the disorder in relation to parturition, as different days-in-milk (**DIM**) can affect the association of SCH with specific disorders. In addition, some studies have used either total Ca or ionized Ca to model the potential associations, which do not necessarily result in the same conclusions. The reader must be aware that just in recent years SCH is being characterized.

Impact of SCH on immune function, uterine disease, and mastitis

Calcium is vital for the performance of innate and adaptive immunity, and responsible for the proliferation, differentiation, and activation of immune cells in response to a stimulus. In dairy cows, the importance of Ca to the innate immune response has been more broadly studied in neutrophils, which are the first line of defense in uterine infections. Low blood Ca is associated with a reduced concentration of Ca in the cytosol of immune cells, leading to a weak response to infectious diseases in early lactation (Kimura et al., 2006; Martinez et al., 2012). Induced SCH in multiparous cows resulted in neutrophil decreased cytosolic Ca concentration, phagocytosis, and oxidative burst (Martinez et al., 2014). Therefore, it is plausible to think that the extracellular Ca pool can influence the ability of neutrophils to perform their phagocytic activity in the postpartum uterus.

Martinez et al. (2012) classified cows as having low and high risk of developing metritis and those with SCH in any of the first 3 DIM had a greater incidence of the disease. Neves et al. (2018a) found an association of SCH and uterine diseases in Holstein cows. For primiparous, SCH assessed at 2, 3 and 4 DIM was associated with the risk of metritis. For multiparous cows, SCH classification at 2 and 4 DIM was associated with an increased risk of metritis for 2nd and 3rd or greater parities, respectively. Chamberlin et al. (2013) did not find any association of metritis based on an ionized Ca cut-off of <1.0 mmol/L within 24 hr of parturition. Wilhelm et al. (2017) found that cows in an organic herd with a serum Ca concentration ≤ 2.0 mmol/L within 2 hr of parturition had increased odds of metritis. Recently, Menta et al. (2021) did not find an association of Ca concentrations in the first 3 DIM with metritis in Jersey cows.

Multiple studies found no association of SCH using Ca concentrations obtained in the first 3 DIM and clinical mastitis (Wilhelm et al., 2017; Neves et al., 2018a; Menta et al., 2021). The association of SCH and subclinical mastitis still require research.

Impact of SCH on energy metabolism, ketosis, and displaced abomasum

Since the last century, it is accepted that the primary trigger for insulin secretion is the increased concentration of Ca in the cytosol of the β-cells (Malaisse, 1972). In normal conditions, glucose is transported into pancreatic β-cells through the GLUT2 transporter where specific enzymes (hexokinase IV and hexokinase I) catalyze the conversion of glucose into glucose-6-phosphate. This process leads to increased production of ATP (Assman et al., 2009), depolarization of the cell membrane, opening of the T-type Ca channel, and release of Ca into the cytosol. The increase in cytosolic Ca results in exocytosis of insulin into the bloodstream, as reviewed by Rorsman et al. (2012). In addition, Ca plays an important role as a cofactor in the Krebs's cycle, being essential in the synthesis of ATP. A decreased Ca concentration seems to interfere with the secretion of insulin, which would then impair glucose uptake by insulin-sensitive tissues. In dairy cows, Martinez et al. (2014) demonstrated that cows with induced SCH via EGTA intravenous challenge had decreased insulin, DMI, and rumination levels. Rodriguez et al. (2017) found that cows classified as having SCH between 24 and 48 hr after calving were 5.5 times more likely to develop ketosis in comparison to normocalcemic cows.

SCH is frequently associated with left displaced abomasum (LDA) (Chapinal et al., 2011; Seifi et al, 2011; Neves et al., 2018a). Interestingly, Bach and McArt (2021) found that despite blood Ca concentrations being low at the time of LDA diagnosis, it was not predictive of future milk production or culling risk (i.e., of no prognostic value).

Impact of SCH on milk production

Recent studies have evaluated the temporal association of Ca and milk production. Neves et al. (2018b) found that reduced Ca concentration within 12 hr after parturition is associated with increased milk production in multiparous Holstein cows. In a different cohort study, Neves et al. (2018a) evaluated the effects of SCH in the first 4 DIM in primiparous and multiparous Holstein cows; this work has shed more light on the epidemiology and the temporality of Ca in fresh cows with different production outcomes. Both primiparous and multiparous cows with reduced Ca concentrations in the first DIM had increased milk production. On the other hand, SCH at 4 DIM was associated with decreased milk production. Menta et al. (2021) found a positive association of SCH at 1 and 2 DIM with milk production in multiparous Jersey cows. In a large herd-level study, Chapinal et al. (2012) demonstrated a negative impact of SCH 1 week prior to and 1 week after calving with milk production. Two recent studies demonstrated that cows having a transient SCH (i.e., cows that achieved normocalcemia by 4 DIM) were the highest milk producers (McArt and Neves, 2020; Seely et al., 2021).

Impact of SCH on reproductive performance

Like early-lactation diseases, different studies used different timepoints of Ca assessments to evaluate the association of SCH with reproductive performance. A cohort study using cows having a persistent SCH-state in the first 3 DIM demonstrated reduced odds of early resumption of ovarian cyclicity and decreased pregnancy at first insemination (Caixeta et al., 2017). Chapinal et al. (2012) demonstrated that SCH at 1 week after calving was associated with lower odds of pregnancy to first insemination. Martinez et al. (2012) and Venjakob et al. (2018) reported increased days open for cows classified as SCH when compared to normocalcemic cows. However, other studies have also demonstrated no association between reproduction outcomes and SCH (Chamberlin et al., 2013; Neves et al., 2018b; Menta et al., 2021); those studies vary in sample size, cow breed, and time of Ca assessment. Larger studies like Chapinal et al. (2012) and Venjakob et al. (2018) seem to better support an association of lower Ca concentration in the postpartum with detrimental reproductive efficiency.

Conclusion

The transition period continues to be a challenging time in the lactation cycle of the dairy cow, and a Ca imbalance seems to be a common risk factor to many fresh cow disorders. Requirements for energy and minerals increase to support colostrogenesis and milk production, and the fresh cow must cope with those demands during a time that many dietary and environmental (management) changes are occurring. Unfortunately, not all cows can correctly or optimally adapt to those demands in a timely fashion and succumb to disease(s), and(or) fail to perform up to their genetic potential. Currently, a lot of debate exists on whether Ca is the primary disorder or a consequence of an underlying issue. Despite that, Ca assessments can indicate a bigger problem and should at least help dairy nutritionists and veterinarians put more emphasis on transition cows in problem herds.

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