**ABSTRACT**

Milk fever is one of the most historically relevant diseases of dairy cows. It is caused by tremendous calcium (Ca) expenditure at the initiation of lactation, so severe that cows can no longer stand and, if left untreated, die. Fortunately, through prepartum nutritional improvements, this version of clinical hypocalcemia is rare in the United States. Nonetheless, the opinion that all versions of postpartum hypocalcemia are detrimental remains pervasive, which is particularly significant given that 50% of cows are subclinically hypocalcemic after calving. This has led to a variety of available management and treatment strategies, ranging from prepartum dietary programs to postpartum Ca gels and boluses, targeted at preventing hypocalcemia in dairy cows. Recent research has determined that postpartum dairy cows can experience different types of subclinical hypocalcemia: transient, persistent, or delayed. We now know cows experiencing transient hypocalcemia as part of the homeorhetic adaptation to lactation are the highest milk producers in modern dairy herds, whereas cows with hypocalcemia several days after calving experience disease and losses in milk production. Therefore, it is wrong to assume all postpartum hypocalcemia is detrimental and that treatment of all cases is considered necessary and beneficial. Research indicates that milk synthesis at the onset of lactation contributes to immediate postpartum hypocalcemia, and that the mammary gland is a critical factor in management of Ca homeostasis. However, cows differ in their ability to manage this phenomenon, and it is possible that immediate postpartum influences such as dry matter intake, inflammation, and immune activation affect appropriate Ca regulation in the days following calving.

**Key words:** hypocalcemia, transient hypocalcemia, dyscalcemia

**Perspective: Transient postparturient hypocalcemia—A lactation-induced phenomenon of high-producing dairy cows**

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**Transient Hypocalcemia Versus Dyscalcemia**

Postpartum cows experience different forms of subclinical hypocalcemia that can be distinguished as transient, persistent, or delayed, and only persistent and delayed hypocalcemia are associated with detrimental effects to health and milk production (McArt and Neves, 2020). Cows with these 2 types of hypocalcemia have an increased risk of early lactation diseases such as metritis, hyperketonemia, displaced abomasa, and herd removal compared to cows that are normocalcemic or transiently hypocalcemic. For example, multiparous cows with persistent or delayed hypocalcemia averaged a 14% incidence of metritis compared with only 4% found in transiently hypocalcemic cows (McArt and Neves, 2020). Further, cows that undergo a transient hypocalcemia produce more milk than cows experiencing any other type of hypocalcemia, as well as cows that remain normocalcemic. The greatest difference in production losses can be seen in cows with delayed hypocalcemia, which produced an average of 8 kg less milk per day across the first 6 to 10 wk of lactation, compared to transiently hypocalcemic cows (McArt and Neves, 2020; Seely et al., 2021). We can differentiate these types of postpartum subclinical hypocalcemia into 2 main groups, transient versus dyscalcemic, based on a blood Ca concentration threshold at 4 DIM regardless of Ca concentration on d 1. Cows with dyscalcemia, whether they have persistent or delayed reductions in Ca concentrations, have detrimental health, production, and reproductive outcomes that differentiate them from normocalcemic or transiently hypocalcemic cows (McArt and Neves, 2020; Seely et al., 2021; Seely and McArt, 2023).

We hypothesize that transient hypocalcemia is critical for both optimal milk production and health of dairy cows, and that the mammary gland plays a central role in this phenomenon. We additionally hypothesize that dyscalcemia is a marker of lactational maladaptation, the cause of which is currently unknown but likely multifactorial. Studies assessing the longitudinal
relationship of milk yield, DMI, inflammation, and immune activation are needed to further evaluate this cause. Additionally, studies focused on transport of Ca into the mammary gland, and subsequently into milk, are critical to understanding the role of the mammary gland in peripartal Ca homeostasis.

**Transient Hypocalcemia Initiates Ca Homeostasis in High-Producing Cows**

It is well established that milk synthesis rapidly depletes Ca from circulation, but the role of the mammary gland in regulation of postparturient Ca homeostasis in dairy cows is unclear. This gap in knowledge could be critical for determining differences in the presentation of transient hypocalcemia versus dyscalcemia in periparturient cows, given that decreased blood Ca concentrations only occur in cows that produce colostrum and milk, compared with those that are mastectomized (Goff et al., 2002). Further, it will likely highlight the physiological mechanisms that result in the increased milk production observed in transiently hypocalcemic cows.

High-producing cows experience transient subclinical hypocalcemia in the immediate postpartum period (Neves et al., 2018; Venjakob et al., 2019; Couto Serrenho et al., 2021). We believe this might be due to elegant control of the cow’s physiology by the mammary gland, triggering quick and robust negative feedback responses to maintain Ca homeostasis and homeorhesis, initiating a transient hypocalcemia. But is this transient hypocalcemia important? In a controlled experiment, we demonstrated that elimination of transient hypocalcemia is detrimental to achieving Ca homeostasis. We treated multiparous cows immediately after parturition with Ca gluconate or a control solution (5% dextrose) intravenously for 24 h to maintain eucalcemia and prevent the typical decrease in Ca concentration at parturition. Interestingly, cows infused with Ca gluconate exhibited a substantial and long-lasting decrease in circulating ionized Ca concentrations immediately after cessation of the Ca infusion, which was more severe than the transient hypocalcemia observed in the control infused cows (M. K. Connelly and L. L. Hernandez; University of Wisconsin–Madison, Madison, WI; unpublished data).

The origin of the role of transient hypocalcemia as a physiological process that results in optimal milk production and cow health is not well defined. However, we do know that the mammary gland of a lactating dairy cow plays a critical role in regulation of maternal Ca homeostasis and initiates physiological adaptations required to support high milk production. To date, the main research on this topic was conducted by Goff et al. (2002), who demonstrated that mastectomized dairy cows did not have a decrease in blood Ca as seen in dairy cows with intact udders. These data suggest that maternal Ca metabolism during lactation is regulated by milk production; however, questions remain as to how to manage Ca homeostasis or homeorhesis during the periparturient period. To this end, we have performed several controlled experiments to determine the role of the mammary gland in transient hypocalcemia.

To further investigate differences in Ca homeostasis in cows with and without active mammary regulation, we used the EGTA model to induce subclinical hypocalcemia for 24 h in nonlactating, nonpregnant as well as early lactation cows 5 to 15 DIM (Connelly et al., 2022). We found it was more difficult to maintain subclinical hypocalcemia in early lactation cows, which became more evident over the course of the 24 h, as the infusion rate of EGTA needed to be increased from ~400 mL/h to ~600 mL/h starting at 9 h and then again to ~800 mL/h at 17 h. Even with the increased rate of EGTA infusion and greater total volume of EGTA infused, lactating cows did not experience hypocalcemia as substantially as nonlactating cows. Nonlactating, nonpregnant cows required a relatively constant infusion rate of EGTA to maintain hypocalcemia over 24 h. Interestingly, at the end of EGTA challenge, early lactation cows had a more rapid increase and sustained elevation in ionized Ca concentrations for 48 h postchallenge, whereas the nonpregnant, nonlactating cows did not. This emphasizes the powerful ability of mammary-derived Ca regulators to assist with recovering hypocalcemia during lactation.

### DMI, INFLAMMATION, AND IMMUNE ACTIVATION

We postulate that transient postpartum hypocalcemia is indicative of a high-producing cow with high DMI that are adapting well to the challenges of early lactation. In addition to the greater milk production and lower early lactation disease incidence described above (McArt and Neves, 2020), we have identified differences in DMI between cows with distinct postpartum Ca dynamics (Seely et al., 2021). In a retrospective study, we found no difference in prepartum DMI between transient and dyscalcemic cows; however, cows with transient hypocalcemia had 15% greater postpartum intake than cows with dyscalcemia. Our findings suggest that high DMI in the immediate postpartum period is an important factor in resumption of normal blood Ca concentrations by 4 DIM, the critical time to avoid the negative implications of milk loss and disease.

Although scientists have postulated on the sequence of events leading to a poor transition into lactation...
(Bradford et al., 2015; Horst et al., 2005), it is unknown if reduced DMI or excessive inflammation via a proinflammatory immune response is a driver of altered Ca homeostasis, or if one or multiple events lead to a reduction in intake and several other physiological events that converge, resulting in dyscalcemia. Increases in postpartum blood haptoglobin concentrations, a marker of inflammation, are apparent in all cows at 3 DIM, but greater elevations for a prolonged period are found in cows that develop metritis compared with cows that remain clinically healthy (Huzzey et al., 2007). We also know that healthy cows have greater blood Ca concentrations at 3 DIM compared with cows that develop metritis, although this is an associative finding (Martinez et al., 2012; Venjakob et al., 2019). This relationship between inflammation and Ca homeostasis is potentially entwined with immune activation; however, this remains correlative, and it is unclear how large a role inflammation may play. Increased haptoglobin concentrations have been measured in response to disease and dystocia, but if the increase is before the presentation of a disease, this could be due to systemic inflammation, which has yet to be demonstrated (Bertoni et al., 2008; Bradford et al., 2015; Nightingale et al., 2015).

Through development and validation of an intravenous LPS challenge model in early lactation cows, Cornell researchers Sabine Mann and Tawny Chandler determined that acute immune activation affects Ca status, such that induction of a proinflammatory response results in a substantial, but short-lived drop in blood Ca concentrations (Chandler et al., 2022b). Previous work had only demonstrated this in mid-late lactation dairy cows (Waldron et al., 2003). It is thus possible that dyscalcemia is instigated by inflammatory responses following immune activation either due to pathogen insult or chronic inflammation in postpartum cows, which leads to production losses. Preliminary data from this group clearly show a negative effect of a proinflammatory mediator, tumor necrosis factor (TNF), on milk production following LPS challenge, with cows experiencing a higher peak plasma TNF concentration and a greater TNF: interleukin-10 ratio having the largest reduction in milk yield on the day of LPS challenge. In addition to the above effects on Ca concentrations and milk production, cows challenged with intravenous LPS had the largest reduction in dry matter intake on the day of the challenge (Chandler et al., 2022a). Although this work and previous work in dairy cows in other stages of lactation suggest an influence of inflammation on the calcium axis, it remains unclear how much the inflammatory process contributes to the regulation of calcium homeostasis in early lactation.

**HOW DO WE PROCEED?**

Collectively, our research in interventional models, as well as in observational research studies, indicates that transient hypocalcemia is a critical observation for optimal milk production, and that transiently hypocalcemic cows have improved postpartum feed intake and health. Further, our research supports the phenomenon that the synthesis of colostrum and milk are largely responsible for governing Ca homeostasis during the peripartal period. These findings necessitate rethinking if, how, and when we should prevent or treat subclinical hypocalcemia. It is possible that our current approaches to postpartum subclinical hypocalcemia prevention, mainly the administration of exogenous Ca, might impair health and production of transiently hypocalcemic cows, whereas dyscalcemic cows might require targeted management and treatment strategies for optimal outcomes. We should consider being more judicious about our postpartum treatment strategies and timing of blood Ca sampling given the need for transient hypocalcemia to appropriately regulate Ca homeostasis. More research on appropriate intervention strategies for cows experiencing dyscalcemia is needed, and future research should focus on understanding the etiologies of dyscalcemia and how to adapt our management strategies to ensure optimal cow health and performance. To this end, our work of late is focused on understanding the biological and physiological mechanisms underpinning the presentations of transient hypocalcemia versus dyscalcemia and how we can better adapt our management and treatment strategies to ensure that cows remain productive and healthy.

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