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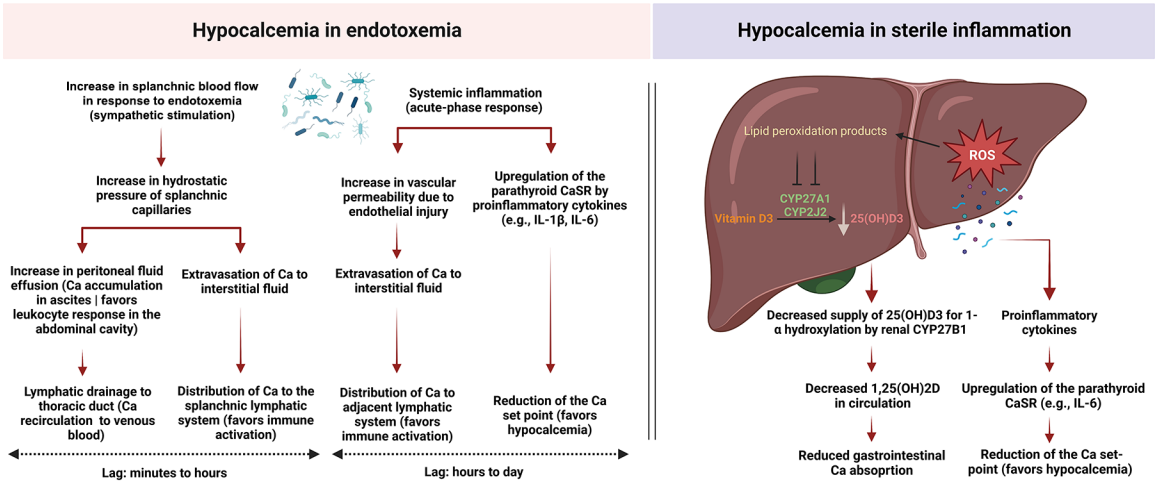
Symposium Review
Health, Behavior, and Well-being

Relationship between calcium dynamics and inflammatory status in the transition period of dairy cows*

Rafael C. Neves†

Graphical Abstract



Summary

Proposed mechanisms linking (1) systemic inflammation during endotoxemia (i.e., presence of lipopolysaccharide in the bloodstream) to hypocalcemia, and (2) systemic inflammation during a sterile inflammatory response to hypocalcemia. Of note, hypocalcemia in the context of this review is defined as a state of significantly reduced blood Ca concentration when Ca concentrations are compared with healthy cows within the same age and stage of lactation (i.e., subclinical hypocalcemia). The reduction of the Ca set-point is defined as the extracellular Ca concentration at which secretion of parathyroid hormone is half-maximal. CaSR = Ca sensing receptor; 25(OH)D3 = 25-hydroxyvitamin D_3; 1,25(OH)2D = 1,25-dihydroxyvitamin D_3; ROS = reactive oxygen species. Figure created with BioRender.com.

Highlights

- Use of blood Ca dynamics in the early postpartum period can help reveal more clear associations between the degree of the systemic inflammatory response after parturition and subclinical hypocalcemia.
- Calcium compartmentalization is the least appreciated component and most likely determinant of hypocalcemia in response to endotoxemia.
- Studies are needed to characterize the relative contribution of endotoxemia versus a sterile inflammatory response in the systemic inflammation observed in transition dairy cows.
- Liver cytochrome P450 enzyme promiscuity could favor eicosanoid production during systemic inflammation over vitamin D hydroxylation and affect Ca metabolism.

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Abstract: Improvements in nutrition, management, and genetics of dairy cows over the last several decades have shifted research focus from clinical diseases to subclinical disorders, to which transition cows are particularly vulnerable. Recent studies on the characterization of subclinical hypocalcemia (SCH) indicate that the combined analysis of the degree, timing of suboptimal blood Ca concentration, and duration are most reflective of the disorder. Therefore, the understanding of blood Ca dynamics in early postpartum cows has emerged as an avenue to investigate the paths leading to a successful metabolic adaptation to lactation or not. The conundrum has been in defining whether SCH is the cause or a reflection of a greater underlying disorder. Immune activation and systemic inflammation have been proposed to be the root cause of SCH. However, there is a paucity of data investigating the mechanisms of how systemic inflammation can lead to reduced blood Ca concentration in dairy cows. The objective of this review is to discuss the links between systemic inflammation and reduced blood Ca concentration, and studies needed to advance knowledge on the interface between systemic inflammation and Ca metabolism for the transition dairy cow.

More than 70 years have passed since a review paper by Hibbs (1950) elegantly discussed several theories for the causes of clinical hypocalcemia (also referred to as milk fever or parturient paresis). Surprisingly, the etiology of clinical hypocalcemia has not been determined yet. In contrast, our knowledge of predisposing factors and the refinement of prepartum nutritional strategies have expanded considerably. Currently, a silent form of the disorder, subclinical hypocalcemia (**SCH**), is a heated research subject and cause of controversy as some groups consider SCH a reflection of a greater disorder rather than a primary issue. A major goal of this short review is to highlight and discuss potential determinants of SCH for the postpartum dairy cow while identifying areas of greater research need. Throughout the paper, the terms hypocalcemia and reduced blood Ca concentration are used interchangeably to denote a state of blood Ca reduction (unrelated to milk fever). Moreover, it does not imply a true deficiency but, to the best of the author's knowledge, a physiological response.

As clinical hypocalcemia is now well prevented, recent analyses of the association of plasma Ca concentration within the traditionally accepted 24 h after parturition unearthed that reduced plasma Ca concentrations at that time point can be associated with increased levels of milk production (Neves et al., 2018b); this same finding has been reported in studies performed across geographical regions and dairy breeds (Venjakob et al., 2018; Menta et al., 2021). As epidemiology works with the accumulation of evidence, those studies demonstrate that the traditional understanding and acceptance that reduced plasma Ca concentration in the first 24 h after calving is consistently detrimental to cow health must be revised.

Decreased blood Ca concentrations had more evident associations with increased disease incidences and production losses when present at 3 to 4 DIM (Neves et al., 2018a). McArt and Neves (2020) hypothesized that potentially 4 subpopulations of cows exist, as follows: (1) cows that can maintain increased blood Ca concentration in the first and fourth DIM (referred to as normocalcemic); (2) cows that have a more pronounced decrease in blood Ca concentration in the first DIM but are normocalcemic by 4 DIM (referred to as having a transient SCH); (3) cows that have reduced blood Ca concentration the first day after parturition and that fail to attain normocalcemia by 4 DIM (referred to as those resembling a persistent SCH); and (4) cows that have average blood Ca concentration for their parity on DIM 1 but that have a decreased blood Ca concentration by 4 DIM (referred to as those resembling a delayed SCH). It is important to note that the SCH classification proposed by McArt and Neves (2020) is only suggestive of how Ca dynamics could help dairy scientists understand the disorder. More studies are necessary using a greater population of cows and herds, and different management systems and geographical distribution to validate those findings. For instance, Tsiamadis et al. (2021), using a cluster-based statistical analysis, suggested that a subclassification into 7 different SCH patterns based on serum Ca concentration collected at 1, 2, 4, and 8 DIM after calving could better explain disease risk across cow parities. Different SCH patterns are conceivable and it is evident that biological variability across cows within a herd and between herds occur; however, there is now more consistent evidence that the degree and duration that cows stay under suboptimal plasma Ca concentrations can help discern a successful from a potentially pathological endocrine adaptation to

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lactation. Moreover, suboptimal blood Ca concentrations by 3 to 4 DIM and onward are consistently reflective of lost production for the dairy cow. The challenge has been in defining whether SCH is the cause or simply the consequence of a greater issue (with systemic inflammation being a major cause). In a study using a convenience sample and pre-collected data from feeding trials and robust longitudinal blood mineral analyte measurements and DMI, Seely et al. (2021) demonstrated that cows classified as having a persistent or delayed SCH (based on McArt and Neves, 2020 classification) had no discernible changes in DMI in the prepartum period. However, meaningfully lower DMI of the persistent and delayed SCH patterns compared with normocalcemic cows was found in the postpartum. Unfortunately, data on markers of systemic inflammation are not available in Seely et al. (2021); however, one may hypothesize that cows classified as having a persistent or delayed SCH could have been afflicted by a higher degree of systemic inflammation compared with normocalcemic cows. Systemic inflammation is well known to be associated with anorexia (Nilsson et al., 2017). Studies that longitudinally follow cows in the prepartum and postpartum with DMI, plasma Ca concentrations, and markers of systemic inflammation could help elucidate the association of the degree of the inflammatory response observed in the prepartum and postpartum period with plasma Ca dynamics after parturition.

It is well known that cows with clinical infectious diseases such as metritis and *Escherichia coli* mastitis have a degree of hypocalcemia. Also, it has been proposed that LPS translocated from the gastrointestinal tract (leaky gut), the uterus, or the mammary gland into systemic circulation results in endotoxemia and associated inflammation; this condition could be prevalent in periparturient cows. If true, a degree of endotoxemia could help explain the link with reduced blood Ca concentration. In human medicine, several hypotheses have been proposed to account for the development of hypocalcemia during endotoxemia. The following hypotheses are of relevance in the context of the transition dairy cow and merit consideration: (1) increased urinary Ca excretion, (2) decreased intestinal Ca absorption, (3) rapid shift in extracellular to intracellular Ca, (4) Ca compartmentalization/sequestration, and (5) increase in calcitonin-related peptides.

Urinary fractional excretion of Ca was decreased during an intravenous LPS infusion in horses and rats (Nakamura et al., 1998; Toribio et al., 2005). In recent postpartum cows, intravenous LPS infusion did not alter the urinary fractional excretion of Ca (Chandler et al., 2022). Currently, no data support an increase (loss) or reduction (conservation) in urinary fractional excretion of Ca during endotoxemia in cows. However, the urine Ca pool in early lactation cows is small and unlikely to be a determinant in the variability of plasma Ca concentration.

A commonly proposed contributor to hypocalcemia during endotoxemia has been a decrease in intestinal Ca absorption. In humans, the transient receptor potential cation V, member 6 (TRPV6) expressed in the duodenum and jejunum is the rate-limiting channel modulating transcellular Ca transfer (active absorption) from the luminal space into the enterocyte (Walters et al., 2006; Lieben et al., 2010). For the ruminant, the rumen is a major organ in transcellular Ca flux (compared with duodenum and jejunum), with the transient receptor potential cation V, member 3 (TRPV3) channel being the major contributor (Schröder et al., 2015; Schrapers et al., 2018). However, it is unknown whether luminal LPS affects TRPV3 activity or if systemic inflammation alters *TRPV3* expression. For instance, TRPV3 was insensitive to LPS in HEK293T cells transfected with mouse *TRPV3* although it was sensitive to a known agonist (Alpizar et al., 2017). It is less likely that a decrease in transcellular Ca movement is a major component of hypocalcemia during endotoxemia as the rumen is constantly exposed to LPS under physiological conditions. Alteration in paracellular Ca movement (passive absorption) during endotoxemia is also unknown in cattle. It seems plausible that the disruption of tight junction proteins and increased gut leakiness during endotoxemia (Bein et al., 2017) would favor an increase in paracellular Ca movement. Despite that, gastrointestinal Ca absorption was not altered in recent postpartum dairy cows submitted to an intravenous LPS challenge (Chandler et al., 2022).

Calcium ion is a major intracellular messenger and directly participates in various cell functions including leukocyte activation (Vig and Kinet, 2009). Therefore, it has been proposed that during states of immune activation (endotoxemia and sepsis, for instance), a greater influx of Ca occurs into immune cells to mediate their response; this theory has been widely proposed to explain a state of hypocalcemia during immune activation. Within the cell, increased concentrations of Ca in the cytosol and endoplasmic reticulum are evident during endotoxemia (He et al., 2020). Significant increases in Ca concentrations were observed in the heart, spleen, liver, kidney, and brain during endotoxemia in rats (He et al., 2020). Also, increased uptake and Ca content in skeletal muscle were found in sepsis models in rodents (Benson et al., 1989), though not evident in swine skeletal muscle collected from a single site (Carlstedt et al., 2000). It is plausible that Ca uptake by skeletal muscle in cattle increases during systemic inflammation to supply AA to the activated immune system; however, the Ca requirement to support muscle proteolysis during systemic inflammation is likely marginal. As extracellular Ca is maintained at several orders of magnitude lower than intracellularly, the influx of Ca occurring in immune cells and skeletal muscle is unlikely to be a major contributor to hypocalcemia during endotoxemia.

Calcium compartmentalization (or redistribution) is likely the greatest factor implicated in the rapid decrease in plasma Ca during endotoxemia and the least appreciated component in human and veterinary medicine. However, it is still unknown what major organs and sites contribute to Ca sequestration in cattle. A reduction in plasma volume, hypovolemia, is characteristic of early-phase endotoxemia. Intravenous infusion of LPS to induce endotoxemia in swine caused a significant increase in Ca in ascites (Carlstedt et al., 2000). Splenectomized rats were able to maintain plasma volume during an intravenous LPS challenge, whereas a significant increase in fluid efflux (measured by the difference in splenic arterial minus splenic venous blood flow) occurred in intact animals (Andrew et al., 2000). An 8-fold increase in spleen lymph flow was demonstrated in a cannulated efferent lymphatic drainage model during LPS challenge in rats (Semaeva et al., 2010). It is unknown if a similar plasma efflux mechanism exists in cattle but, if so, would help explain the sudden decrease in plasma Ca concentration following LPS challenge models. However, it is more likely that the redistribution of blood flow to splanchnic organs and vasodilation occurring during endotoxemia (Fong et al., 1990) promotes increased capillary splanchnic pressure and extravasation of Ca to the interstitium and ascites. Also, it is plausible that major lymphoid organs like the spleen would favor Ca sequestration

for immune cell activation and differentiation for a whole-body response. Fluid extravasation from the microvasculature in the abdominal region was observed in a septic shock model in baboons using technetium-99m-labeled albumin (Dormehl et al., 1992). Endothelial cell permeability increases during endotoxemia (Ince et al., 2016); this would increase and maintain fluid extravasation to the interstitium and could help explain the maintenance of hypocalcemia during endotoxemia. Use of radioisotopes such as technetium-99m-labeled calcium gluconate could be used as a means to evaluate calcium sequestration in a bovine model of endotoxemia using imaging integrated systems based on single photon emission computed tomography and computed tomography (SPECT/CT). In addition, it is known that proinflammatory cytokines like IL-1β and IL-6 regulates the Ca sensing receptor (CaSR) in the parathyroid to decrease the Ca set-point (i.e., a mechanism that would favor a reduction in extracellular Ca concentration; Toribio et al., 2003; Canaff et al., 2008).

A major protein involved in bacterial sepsis and commonly thought to be a contributor to the hypocalcemic response is procalcitonin (i.e., the precursor protein of the hormone calcitonin). Calcitonin (but not procalcitonin) is the main protein responsible for increasing renal Ca excretion and inhibiting osteoclast activity and bone demineralization. In cattle, procalcitonin is increased during sepsis (Bonelli et al., 2018). Matera et al. (2012) demonstrated that procalcitonin could neutralize bacterial LPS in vitro and modulate the inflammatory response of human peripheral blood mononuclear cells. The role of procalcitonin in contributing to a hypocalcemic response during endotoxemia is questionable though it has been proposed as a potential mechanism in the human literature (Müller et al., 2000). More recently, the use of a mouse knockdown model of the *Calca* gene (procalcitonin gene) revealed that procalcitonin expression in the bone microenvironment impaired early osteoclast formation and bone resorption (Baranowsky et al., 2022). If procalcitonin is severely upregulated in cases of endotoxemia and systemic inflammation in the bone microenvironment of cattle (which is unknown to this date), it could hypothetically contribute to lower bone resorption and favor a more chronic hypocalcemic state. However, there is more evidence that a proinflammatory state favors osteoclast development and activity (Kitaura et al., 2020). Studies evaluating the response of bone to systemic inflammation in cattle are warranted.

The increased Ca requirement for milk production is a significant additive effect to the hypocalcemic stress experienced by the dairy cow during systemic inflammation. Under a healthy state, changes in milking practices (i.e., restricted or delayed milking) in the first 48 h after parturition favored an increase in plasma Ca concentration, for example (Valldecabres et al., 2022). During an intravenous LPS challenge, milk Ca secretion decreased (Chandler et al., 2022). Plasma Ca must turnover several times a day to support milk Ca output and poses a major challenge in the maintenance of Ca concentration in the extracellular fluid for the dairy cow (Horst et al., 1997). Altogether, the hypocalcemic effects during systemic inflammation are likely amplified for the lactating dairy cow compared with species requiring lower plasma turnover to support lactation (e.g., humans).

The term sterile inflammation refers to an inflammatory process that occurs in the absence of microorganisms and is triggered by damaged or necrotic cells, or both (Shen et al., 2013). An imbalance between the production of reactive oxygen species (**ROS**), release of damage-associated molecular patterns, and antioxidant defenses are characteristics of sterile inflammation (Shen et al., 2013). Postpartum cows suffer from a greater degree of redox imbalance compared with the prepartum period as demonstrated by greater plasma concentrations of ROS accompanied by a decrease in total antioxidants. Increased oxidative stress has been associated with a sterile inflammatory process in tissues such as placenta (during parturition) and adipose tissue remodeling (Baker et al., 2021). For the postpartum cow, the liver is a key organ in the adaptive response to increased nutrient demands. Major upregulation of genes involved in oxidative phosphorylation and protein import into the mitochondrial matrix occurs in the postpartum (Gao et al., 2021), which could lead to redox stress and hepatocyte injury (i.e., a sterile inflammatory process). If true, how could such a condition be linked to lower plasma Ca concentrations?

It is well known that ROS induces lipid peroxidation as membrane phospholipids come in contact with oxidizing agents. A direct effect of cholesterol 7-hydroperoxide (a primary product of lipid peroxidation) has been shown to directly reduce the activity of CYP27A1 in an in vitro model using THP-1 macrophages (Korytowski et al., 2015). van Lier et al. (2015) demonstrated that CYP27A1 catalyzed the reduction of cholesterol 25-hydroperoxide to 25-hydroxycholesterol, which presumably would facilitate the removal of those lipid hydroperoxides (oxidative stress byproducts) through bile and avoid the propagation of organ injury. Of note, *CYP27A1* was widely expressed across major tissues in dairy cows though it had its greatest expression in the liver (Kuhn et al., 2020). In humans, CYP27A1 participates in bile acid metabolism and vitamin D hydroxylation (Lorbek et al., 2012). Therefore, it likely has a major role in mediating 25-hydroxylation of vitamin D and bile acid metabolism in cattle as well. To date, it is unknown how liver *CYP27A1* expression changes in transition period dairy cows and under conditions of increased systemic inflammation. However, it is plausible that a level of substrate competition for CYP27A1 activity may occur between oxysterols involved in bile acid biosynthesis, vitamin D_3, and lipid peroxidation products originating from hepatocyte injury (due to oxidative stress). If true, this would decrease vitamin D hydroxylation and impair the vitamin D-Ca axis.

A large whole-genome study identified putative genomic regions harboring *CYP27A1* and *CYP2J2* genes being considerably related to additive genetic variance for clinical hypocalcemia incidence (Pacheco et al., 2018). *CYP2J2* has been suggested as a prime potential gene controlling plasma concentrations of 25-hydroxyvitamin D in cattle (Casas et al., 2013). However, under inflammatory conditions, CYP2J2 has an active role in mediating epoxyeicosatrienoic acid (EETs) production from arachidonic acid (Node et al., 1999). Overexpression of *CYP2J2* in a mouse model of nonalcoholic fatty liver (a disorder sharing some resemblance to fatty liver in cows) reduced liver oxidative stress and inflammatory response (Hendrikx et al., 2015). A strong negative relationship between hepatic triacylglycerol content and plasma Ca concentration assessed in the first 3 d after parturition was recently demonstrated (Arshad and Santos, 2022); this provides evidence for the potential connection between hepatic lipidosis, liver oxidative stress, and systemic inflammation with SCH. Potential substrate competition may occur between arachidonic acid released from cell membrane injury and vitamin D, which could lead to a greater rate of formation of EETs over 25-hydroxyvitamin D. Consequently, the amount

of 25-hydroxyvitamin D available for renal 1-α hydroxylation would be severely compromised, contributing to a vitamin D_3 deficiency. If true, vitamin D_3 deficiency would lead to decreased gastrointestinal Ca absorption and help explain SCH.

Interleukin-6, a major proinflammatory cytokine involved in the upregulation of the CaSR (as previously discussed), is also elevated during sterile surgical procedures (Nishimoto et al., 1989). Therefore, sterile inflammatory processes occurring in the postpartum cow could also favor a decrease in the biological Ca set-point and help explain a degree of SCH in those scenarios.

In conclusion, several mechanisms leading to suboptimal plasma Ca concentration of the periparturient dairy cow during systemic inflammation are identified and knowledge gaps are discussed. It is proposed that sterile inflammation can be a major driver of SCH in postpartum cows, and studies designed to identify and discern major causes of systemic inflammation (endotoxemia vs. sterile inflammation) as drivers of SCH in postpartum dairy cows are needed. Also, research focusing on the characterization of the major CYP450 isoforms participating in vitamin D hydroxylation and eicosanoid biosynthesis in dairy cows, as well as their activity and stereoselectivity, would help determine shared pathways between inflammation and Ca metabolism. Those studies will be fundamental in elucidating potential new pathways to be modulated via nutritional and pharmaceutical methods to favor the metabolic and inflammatory fitness of transition dairy cows.

References

Alpizar, Y. A., B. Boonen, A. Sanchez, C. Jung, A. López-Requena, R. Naert, B. Steelant, K. Luyts, C. Plata, V. De Vooght, J. A. J. Vanoirbeek, V. M. Meseguer, T. Voets, J. L. Alvarez, P. W. Hellings, P. H. M. Hoet, B. Nemery, M. A. Valverde, and K. Talavera. 2017. TRPV4 activation triggers protective responses to bacterial lipopolysaccharides in airway epithelial cells. Nat. Commun. 8:1059. https://doi.org/10.1038/s41467-017-01201-3.

Andrew, P., Y. Deng, and S. Kaufman. 2000. Fluid extravasation from spleen reduces blood volume in endotoxemia. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278:R60–R65. https://doi.org/10.1152/ajpregu.2000.278.1.R60.

Arshad, U., and J. E. P. Santos. 2022. Hepatic triacylglycerol associations with production and health in dairy cows. J. Dairy Sci. 105:5393–5409. https://doi.org/10.3168/jds.2021-21031.

Baker, B. C., A. E. P. Heazell, C. Sibley, R. Wright, H. Bischof, F. Beards, T. Guevara, S. Girard, and R. L. Jones. 2021. Hypoxia and oxidative stress induce sterile placental inflammation in vitro. Sci. Rep. 11:7281. https://doi.org/10.1038/s41598-021-86268-1.

Baranowsky, A., D. Jahn, S. Jiang, T. Yorgan, P. Ludewig, J. Appelt, K. K. Albrecht, E. Otto, P. Knapstein, A. Donat, J. Winneberger, L. Rosenthal, P. Köhli, C. Erdmann, M. Fuchs, K. H. Frosch, S. Tsitsilonis, M. Amling, T. Schinke, and J. Keller. 2022. Procalcitonin is expressed in osteoblasts and limits bone resorption through inhibition of macrophage migration during intermittent PTH treatment. Bone Res. 10:9. https://doi.org/10.1038/s41413-021-00172-y.

Bein, A., A. Zilbershtein, M. Golosovsky, D. Davidov, and B. Schwartz. 2017. LPS induces hyper-permeability of intestinal epithelial cells. J. Cell. Physiol. 232:381–390. https://doi.org/10.1002/jcp.25435.

Benson, D. W., P. O. Hasselgren, D. T. Hiyama, J. H. James, S. Li, D. F. Rigel, and J. E. Fischer. 1989. Effect of sepsis on calcium uptake and content in skeletal muscle and regulation in vitro by calcium of total and myofibrillar protein breakdown in control and septic muscle: results from a preliminary study. Surgery 106:87–93.

Bonelli, F., V. Meucci, T. J. Divers, A. Boccardo, D. Pravettoni, M. Meylan, A. G. Belloli, and M. Sgorbini. 2018. Plasma procalcitonin concentration in healthy calves and those with septic systemic inflammatory response syndrome. Vet. J. 234:61–65. https://doi.org/10.1016/j.tvjl.2018.02.003.

Canaff, L., X. Zhou, and G. N. Hendy. 2008. The proinflammatory cytokine, interleukin-6, up-regulates calcium-sensing receptor gene transcription via Stat1/3 and Sp1/3. J. Biol. Chem. 283:13586–13600. https://doi.org/10.1074/jbc.M708087200.

Carlstedt, F., M. Eriksson, R. Kiiski, A. Larsson, and L. Lind. 2000. Hypocalcemia during porcine endotoxemic shock: Effects of calcium administration. Crit. Care Med. 28:2909–2914. https://doi.org/10.1097/00003246-200008000-00037.

Casas, E., R. J. Leach, T. A. Reinhardt, R. M. Thallman, J. D. Lippolis, G. L. Bennett, and L. A. Kuehn. 2013. A genomewide association study identified CYP2J2 as a gene controlling serum vitamin D status in beef cattle. J. Anim. Sci. 91:3549–3556. https://doi.org/10.2527/jas.2012-6020.

Chandler, T. L., T. A. Westhoff, P. A. LaPierre, T. R. Overton, and S. Mann. 2022. Calcium metabolism following LPS challenge in early postpartum cows maintained at eucalcemia. Page 93 in Proceedings of the American Dairy Science Association Annual Meeting, Kansas City, MO. American Dairy Science Association.

Dormehl, I. C., N. Hugo, J. P. Pretorius, and I. F. Redelinghuys. 1992. In vivo assessment of regional microvascular albumin leakage during *E. coli* septic shock in the baboon model. Circ. Shock 38:9–13.

Fong, Y. M., M. A. Marano, L. L. Moldawer, H. Wei, S. E. Calvano, J. S. Kenney, A. C. Allison, A. Cerami, G. T. Shires, and S. F. Lowry. 1990. The acute splanchnic and peripheral tissue metabolic response to endotoxin in humans. J. Clin. Invest. 85:1896–1904. https://doi.org/10.1172/JCI114651.

Gao, S. T., D. D. Girma, M. Bionaz, L. Ma, and D. P. Bu. 2021. Hepatic transcriptomic adaptation from prepartum to postpartum in dairy cows. J. Dairy Sci. 104:1053–1072. https://doi.org/10.3168/jds.2020-19101.

He, W., L. Huang, H. Luo, Y. Zang, Y. An, and W. Zhang. 2020. Hypocalcemia in sepsis: analysis of the subcellular distribution of Ca^{2+} in septic rats and LPS/TNF-α-treated HUVECs. J. Infect. Dev. Ctries. 14:908–917. https://doi.org/10.3855/jidc.12341.

Hendrikx, T., M. L. Jeurissen, V. Bieghs, S. M. Walenbergh, P. J. van Gorp, F. Verheyen, T. Houben, Y. D. Guichot, M. J. Gijbels, E. Leitersdorf, M. H. Hofker, D. Lütjohann, and R. Shiri-Sverdlov. 2015. Hematopoietic overexpression of Cyp27a1 reduces hepatic inflammation independently of 27-hydroxycholesterol levels in Ldlr(−/−) mice. J. Hepatol. 62:430–436. https://doi.org/10.1016/j.jhep.2014.09.027.

Hibbs, J. W. 1950. Milk fever (parturient paresis) in dairy cows—A review. J. Dairy Sci. 33:758–789. https://doi.org/10.3168/jds.S0022-0302(50)91966-7.

Horst, R. L., J. P. Goff, and T. A. Reinhardt. 1997. Calcium and vitamin D metabolism during lactation. J. Mammary Gland Biol. Neoplasia 2:253–263. https://doi.org/10.1023/A:1026384421273.

Ince, C., P. R. Mayeux, T. Nguyen, H. Gomez, J. A. Kellum, G. A. Ospina-Tascón, G. Hernandez, P. Murray, and D. De Backer. 2016. The endothelium in sepsis. Shock 45:259–270. https://doi.org/10.1097/SHK.0000000000000473.

Kitaura, H., A. Marahleh, F. Ohori, T. Noguchi, W. R. Shen, J. Qi, Y. Nara, A. Pramusita, R. Kinjo, and I. Mizoguchi. 2020. Osteocyte-related cytokines regulate osteoclast formation and bone resorption. Int. J. Mol. Sci. 21:5169. https://doi.org/10.3390/ijms21145169.

Korytowski, W., K. Wawak, P. Pabisz, J. C. Schmitt, A. C. Chadwick, D. Sahoo, and A. W. Girotti. 2015. Impairment of macrophage cholesterol efflux by cholesterol hydroperoxide trafficking: Implications for atherogenesis under oxidative stress. Arterioscler. Thromb. Vasc. Biol. 35:2104–2113. https://doi.org/10.1161/ATVBAHA.115.306210.

Kuhn, M. J., A. K. Putman, and L. M. Sordillo. 2020. Widespread basal cytochrome P450 expression in extrahepatic bovine tissues and isolated cells. J. Dairy Sci. 103:625–637. https://doi.org/10.3168/jds.2019-17071.

Lieben, L., B. S. Benn, D. Ajibade, I. Stockmans, K. Moermans, M. A. Hediger, J. B. Peng, S. Christakos, R. Bouillon, and G. Carmeliet. 2010. Trpv6 mediates intestinal calcium absorption during calcium restriction and contributes to bone homeostasis. Bone 47:301–308. https://doi.org/10.1016/j.bone.2010.04.595.

Lorbek, G., M. Lewinska, and D. Rozman. 2012. Cytochrome P450s in the synthesis of cholesterol and bile acids – From mouse models to human diseases. FEBS J. 279:1516–1533. https://doi.org/10.1111/j.1742-4658.2011.08432.x.

Matera, G., A. Quirino, A. Giancotti, M. C. Pulicari, L. Rametti, M. L. Rodríguez, M. C. Liberto, and A. Focà. 2012. Procalcitonin neutralizes bacterial LPS and reduces LPS-induced cytokine release in human peripheral blood mononuclear cells. BMC Microbiol. 12:68. https://doi.org/10.1186/1471-2180-12-68.

McArt, J. A. A., and R. C. Neves. 2020. Association of transient, persistent, or delayed subclinical hypocalcemia with early lactation disease, removal, and milk yield in Holstein cows. J. Dairy Sci. 103:690–701. https://doi.org/10.3168/jds.2019-17191.

Menta, P. R., L. Fernandes, D. Poit, M. L. Celestino, V. S. Machado, M. A. Ballou, and R. C. Neves. 2021. Association of blood calcium concentration in the first 3 days after parturition and energy balance metabolites at day 3 in milk with disease and production outcomes in multiparous Jersey cows. J. Dairy Sci. 104:5854–5866. https://doi.org/10.3168/jds.2020-19189.

Müller, B., K. L. Becker, M. Kränzlin, H. Schächinger, P. R. Huber, E. S. Nylèn, R. H. Snider, J. C. White, H. Schmidt-Gayk, W. Zimmerli, and R. Ritz. 2000. Disordered calcium homeostasis of sepsis: Association with calcitonin precursors. Eur. J. Clin. Invest. 30:823–831. https://doi.org/10.1046/j.1365-2362.2000.00714.x.

Nakamura, T., Y. Mimura, K. Uno, and M. Yamakawa. 1998. Parathyroid hormone activity increases during endotoxemia in conscious rats. Horm. Metab. Res. 30:88–92. https://doi.org/10.1055/s-2007-978842.

Neves, R. C., B. M. Leno, K. D. Bach, and J. A. A. McArt. 2018a. Epidemiology of subclinical hypocalcemia in early-lactation Holstein dairy cows: The temporal associations of plasma calcium concentration in the first 4 days in milk with disease and milk production. J. Dairy Sci. 101:9321–9331. https://doi.org/10.3168/jds.2018-14587.

Neves, R. C., B. M. Leno, M. D. Curler, M. J. Thomas, T. R. Overton, and J. A. A. McArt. 2018b. Association of immediate postpartum plasma calcium concentration with early-lactation clinical diseases, culling, reproduction, and milk production in Holstein cows. J. Dairy Sci. 101:547–555. https://doi.org/10.3168/jds.2017-13313.

Nilsson, A., D. B. Wilhelms, E. Mirrasekhian, M. Jaarola, A. Blomqvist, and D. Engblom. 2017. Inflammation-induced anorexia and fever are elicited by distinct prostaglandin dependent mechanisms, whereas conditioned taste aversion is prostaglandin independent. Brain Behav. Immun. 61:236–243. https://doi.org/10.1016/j.bbi.2016.12.007.

Nishimoto, N., K. Yoshizaki, H. Tagoh, M. Monden, S. Kishimoto, T. Hirano, and T. Kishimoto. 1989. Elevation of serum interleukin 6 prior to acute phase proteins on the inflammation by surgical operation. Clin. Immunol. Immunopathol. 50:399–401. https://doi.org/10.1016/0090-1229(89)90147-5.

Node, K., Y. Huo, X. Ruan, B. Yang, M. Spiecker, K. Ley, D. C. Zeldin, and J. K. Liao. 1999. Anti-inflammatory properties of cytochrome P450 epoxygenase-derived eicosanoids. Science 285:1276–1279. https://doi.org/10.1126/science.285.5431.1276.

Pacheco, H. A., S. da Silva, A. Sigdel, C. K. Mak, K. N. Galvão, R. A. Texeira, L. T. Dias, and F. Peñagaricano. 2018. Gene mapping and gene-set analysis for milk fever incidence in Holstein dairy cattle. Front. Genet. 9:465. https://doi.org/10.3389/fgene.2018.00465.

Schrapers, K. T., G. Sponder, F. Liebe, H. Liebe, and F. Stumpff. 2018. The bovine TRPV3 as a pathway for the uptake of Na^+, Ca^{2+}, and NH_4^+. PLoS One 13:e0193519. https://doi.org/10.1371/journal.pone.0193519.

Schröder, B., M. R. Wilkens, G. E. Ricken, S. Leonhard-Marek, D. R. Fraser, and G. Breves. 2015. Calcium transport in bovine rumen epithelium as affected by luminal Ca concentrations and Ca sources. Physiol. Rep. 3:e12615. https://doi.org/10.14814/phy2.12615.

Seely, C. R., B. M. Leno, A. L. Kerwin, T. R. Overton, and J. A. A. McArt. 2021. Association of subclinical hypocalcemia dynamics with dry matter intake, milk yield, and blood minerals during the periparturient period. J. Dairy Sci. 104:4692–4702. https://doi.org/10.3168/jds.2020-19344.

Semaeva, E., O. Tenstad, J. Skavland, M. Enger, P. O. Iversen, B. T. Gjertsen, and H. Wiig. 2010. Access to the spleen microenvironment through lymph shows local cytokine production, increased cell flux, and altered signaling of immune cells during lipopolysaccharide-induced acute inflammation. J. Immunol. 184:4547–4556. https://doi.org/10.4049/jimmunol.0902049.

Shen, H., D. Kreisel, and D. R. Goldstein. 2013. Processes of sterile inflammation. J. Immunol. 191:2857–2863. https://doi.org/10.4049/jimmunol.1301539.

Toribio, R. E., C. W. Kohn, C. C. Capen, and T. J. Rosol. 2003. Parathyroid hormone (PTH) secretion, PTH mRNA and calcium-sensing receptor mRNA expression in equine parathyroid cells, and effects of interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha on equine parathyroid cell function. J. Mol. Endocrinol. 31:609–620. https://doi.org/10.1677/jme.0.0310609.

Toribio, R. E., C. W. Kohn, J. Hardy, and T. J. Rosol. 2005. Alterations in serum parathyroid hormone and electrolyte concentrations and urinary excretion of electrolytes in horses with induced endotoxemia. J. Vet. Intern. Med. 19:223–231. https://doi.org/10.1111/j.1939-1676.2005.tb02686.x.

Tsiamadis, V., N. Panousis, N. Siachos, A. I. Gelasakis, G. Banos, A. Kougioumtzis, G. Arsenos, and G. E. Valergakis. 2021. Subclinical hypocalcaemia follows specific time-related and severity patterns in post-partum Holstein cows. Animal 15:100017. https://doi.org/10.1016/j.animal.2020.100017.

Valldecabres, A., R. B. Lopes, A. Lago, C. Blanc, and N. Silva-del-Río. 2022. Effects of postpartum milking strategy on plasma mineral concentrations and colostrum, transition milk, and milk yield and composition in multiparous dairy cows. J. Dairy Sci. 105:595–608. https://doi.org/10.3168/jds.2021-20590.

van Lier, J. E., N. Mast, and I. A. Pikuleva. 2015. Cholesterol hydroperoxides as substrates for cholesterol-metabolizing cytochrome P450 enzymes and alternative sources of 25-hydroxycholesterol and other oxysterols. Angew. Chem. Int. Ed. 54:11138–11142. https://doi.org/10.1002/anie.201505002.

Venjakob, P. L., L. Pieper, W. Heuwieser, and S. Borchardt. 2018. Association of postpartum hypocalcemia with early-lactation milk yield, reproductive performance, and culling in dairy cows. J. Dairy Sci. 101:9396–9405. https://doi.org/10.3168/jds.2017-14202.

Vig, M., and J. P. Kinet. 2009. Calcium signaling in immune cells. Nat. Immunol. 10:21–27. https://doi.org/10.1038/ni.f.220.

Walters, J. R. F., S. Balesaria, K.-M. Chavele, V. Taylor, J. L. Berry, U. Khair, N. F. Barley, D. A. van Heel, J. Field, J. O. Hayat, A. Bhattacharjee, R. Jeffery, and R. Poulsom. 2006. Calcium channel TRPV6 expression in human duodenum: Different relationships to the vitamin D system and aging in men and women. J. Bone Miner. Res. 21:1770–1777. https://doi.org/10.1359/jbmr.060721.

Notes

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