Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.50.007933

Optimizing Calcium Metabolism in Transition Cows: A Pragmatic Review

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ARTICLE INFO

Received: April 26, 2023

Published: May 10, 2023

Citation: Akbar Nikkhah and Masoud Alimirzaei. Optimizing Calcium Metabolism in Transition Cows: A Pragmatic Review. Biomed J Sci & Tech Res 50(2)-2023. BJSTR. MS.ID.007933.

ABSTRACT

Dairy cows undergo tremendous metabolic and endocrine changes during the transition from dry to lactating phase. Hypocalcemia is one of the most critical metabolic conditions that dairy cows experience after calving. The objective of this review article was to underline the role of calcium homeostasis in determining the periparturient dairy cow's health and performance. In addition, nutritional strategies to maintain normal blood calcium levels in fresh cows were addressed. For many years, it has been believed that decreased dry matter intake, insulin levels and tissue sensitivity, increased growth hormone levels as well as inflammation are the most important factors leading to negative energy balance (NEB) and fatty acids release from the adipose tissue to meet energy requirements of transition cows. Failure in adaptation to such metabolic alterations would result in health issues including ketosis, fatty liver, mastitis, and other metabolic and infectious diseases. The role of immune disturbance in inducing NEB and subsequent metabolic and infectious problems has been emphasized more recently. Calcium, as a macro-mineral has fundamental roles in the physiology of transition cows. Suppressed muscle contractility and milk fever are direct consequences of calcium perturbation in postpartum cows. Calcium is likely involved in immune system functioning. Accordingly, traditional insights into calcium metabolism in fresh cows should be revisited, and the role of the extracellular fluid calcium in regulating immune system and transition cow's energetics should be highlighted. Overall, as a golden nutritional goal, alleviating blood calcium depression postpartum may be a useful strategy to minimize post-calving disorders and enhance performance of cows throughout the lactation period.

Keywords: Calcium; Metabolism; Periparturient Cow; Immunity; Metabolic Disorder

Abbreviations: NEB: Negative Energy Balance; NEFA: Non-Esterified Fatty Acids; BHBA: Beta-Hydroxybutyrate; CA: Blood Calcium; PTH: Parathyroid Hormone; DCAD: Dietary Cation-Anion Difference; DMI: Dry Matter Intake; CVAS: Cumberland Valley Analytical Service's; LPS: Lipopolysaccharide

Introduction

After calving, energy output from milk is greater than food energy intake. Thus, fresh cows are exposed to negative energy balance (NEB). The severity of NEB may determine whether fresh cows will develop post-calving disorders or not. In severe cases, fatty acids are released from the adipose tissue leading to elevated levels of non-esterified fatty acids (NEFA) and beta-hydroxybutyrate (BHBA) and finally may cause metabolic disorders such as fatty liver and ketosis [1]. In addition to the disturbances in fresh cows' energetics, blood calcium (Ca) concentration drops following the onset of lactation to support colostrum and milk production resulting in NEB [2]. The sudden depletion of the extra-cellular fluid's Ca would result in hypocalcemia that may lead to the clinical form of hypocalcemia or milk fever if the Ca depletion is severe. The relationships between NEB, plasma NEFA, hypocalcemia and related metabolic and infectious diseases has been recently discussed [3]. Despite the association between higher levels of NEFA and metabolic disorders, immune dys-

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function in periparturient cows seems to be the main cause of NEB in fresh cows. Inflammation and immune activation are proposed as causatives of NEB post-calving. Since plasma Ca levels are decreased during inflammatory states [3], it can be hypothesized that blood Ca concentrations possess an important role in immune system regulation. The response of immune cells to stimuli decreases following hypocalcemia [4]. Impaired neutrophil function and altered metabolism were reported using Ca chelates and induced hypocalcemia in dairy cows [5]. More recently, Horst, et al. [6] suggested that hypocalcemia could be alleviated using Ca administration in cows challenged by lipopolysaccharide (LPS). Therefore, Ca metabolism and its critical role in fresh cow's immune function should be considered when formulating nutritional strategies on-farm.

Calcium Homeostasis, Hypocalcemia, and Consequences

Maintaining normal Ca levels in extracellular and intracellular fluids is critical for many physiological functions in human and animals. It is well known that the extracellular Ca drops following the onset of lactation which is defined as sub-clinical (< 8.5 mg/dl; about 30-50% of fresh cows) and clinical (<7.5 mg/dl; about 5% of fresh cows) mg/dl) hypocalcemia [2]. The latter is also called milk fever [2]. Plasma Ca is closely involved in different physiological processes including muscle contractility, bone mineralization, intermediary metabolism, cell signalling, and immune function, tightly controlled by several mechanisms [7]. In periparturient cows, several organs such as bones, kidneys, and the gastrointestinal tract as well as the parathyroid hormone (PTH) regulate Ca homeostasis [7]. Calcium requirements of dairy cows increase remarkably (>65%) in line with lactation predisposing fresh cows to different degrees of hypocalcemia [8]. As the extracellular calcium levels decline, PTH is secreted in response to dropping Ca levels to restore Ca reserves via three ways:

1. Increasing renal Ca reabsorption,
2. Triggering bones to release Ca, and
3. Stimulating kidneys to produce 1,25-dihydroyvitamin D (calcitriol) [3].

Calcitriol, then, accompanied by PTH stimulates Ca transport across the intestinal epithelial cells. Transcellular and paracellular pathways are proposed for Ca absorption from the gastrointestinal tract. Failure of such mechanisms to return and maintain normal plasma Ca concentrations would lead to hypocalcemia and milk fever [3].

As noted above, approximately 50% of dairy cows suffer from hypocalcemia after parturition. It is important to note that from a herd health viewpoint, the subclinical hypocalcemia could be more harmful than the clinical form because of greater incidence of other diseases such as displacement abomasum, retained placenta, ketosis, metritis, mastitis, and various early lactation disorders [9]. Hypocalcemic cows are 3-5 times more likely to develop postpartum diseases and have 50% more culling rate in early lactation [10]. In addition to health issues, it seems that hypocalcemia may adversely affect fertility in dairy cows [7]. Moreover, conception rate to first service was lower in hypocalcemic cows vs. normocalcemic cows [7]. It seems that the time during which blood Ca remains below 8.5 mg/dl and cows experience hypocalcemia may predispose cows to detrimental effects of hypocalcemia [11]. In a survey to determine the importance of hypocalcemia length on subsequent disease prevalence, cows with plasma Ca concentrations of ≤2.15 mmol/L on d 1, 2, and 3 postpartum showed 70% reduced odds of conception per firs service [12]. Persistency of hypocalcemia for about 2 and 4 days in milk in primiparous and older cows was associated with increased disease incidence and reduced milk production in early lactation [9,13]. More recently, sub-clinical hypocalcemia at d 4 of lactation was associated with reduced reproductive performance [11]. Hence, the duration of sub-clinical hypocalcemia is more important than the absolute reduction of plasma Ca levels.

Nutritional Management of Prepartum Cows

Dietary Strategies and Feed Characteristics

A successful transition period requires targeted nutritional strategies. During the time that feed intake is depressed, and metabolic processes are changing, optimizing the Ca metabolism should be considered when formulating diets for transition cows. It is believed that acidifying the prepartum rations by feeding anionic salts could reduce the risk of hypocalcemia in postpartum cows [14]. The concept of dietary cation-anion difference (DCAD) is used to determine the acid-base status of dry or lactation rations. The DCAD is calculated by subtracting the total diet anions including chloride (Cl^-) and sulfate (S^{-2}) form the total diet cations including sodium (Na^+) and potassium (K^+) [2]. Negative DCAD is thought to be effective in inducing metabolic acidosis that may increase Ca flux due to increased renal Ca reabsorption and tissues sensitivity to PTH [2]. As a result, cows can properly respond to Ca challenges immediately after calving. Decreasing the DCAD of prepartum cows using anionic salts linearly increased plasma Ca levels and increased dry matter intake (DMI) and milk yield postpartum [15]. However, it seems that further reduction of DCAD may have no advantages or could even adversely affect the health of both dam and the newborn calf [16]. Reducing DCAD from +300 to -200 mEq/kg DM depressed DMI, caused severe metabolic acidosis, increased displacement abomasum rate, impaired fertility, and negatively affected cow health in early lactation [17,18]. As noted, lower DCAD causes metabolic acidosis in prepartum cows.

The severity of metabolic acidosis under different DCAD values can be assessed by measuring urinary pH [16]. The urinary pH ranged from 6.0 to 6.8 has been proposed as optimum pH, reflecting mild metabolic acidosis [16]. Urinary pH below 6.0 is an indicator of severe metabolic acidosis which would be detrimental from a health viewpoint [16,18]. In addition to the absolute low DCAD values, duration of feeding negative DCAD may also affect health and productivity of lactating cows. In some studies [19,20], the extended feeding of negative DCAD diets had no effects on cow health and performance postpartum. However, in a study conducted to examine the relationships between the severity of acidification (DCAD = -7mEq/100 g DM vs. -18 mEq/100 g DM) and its feeding duration (21 vs. 42 d prepartum), feeding the lower DCAD diet reduced prepartum DMI [21]. Additionally, feeding negative DCAD diets for an extended period decreased milk yield for about 2.5 kg/d [21]. In a recent meta-analysis, decreasing dietary DCAD from +20 to -10 mEq/100 g DM resulted in reduced DMI by 0.7 kg/d in mulrtiparous and 0.4 kg/d in primiparous cows [17]. In research to determine the cause of depressed feed intake under low DCAD, metabolic acidosis, and not just adding anionic salts, was proposed as the main mediator of depressed feed intake [22].

Feeding low-calcium diets prepartum is another strategy to stimulate PTH secretion in prepartum cows in which prepartum cows are adapted to low plasma Ca with an artificially induced hypocalcemia for a short period. It is believed that such a feeding strategy may contribute to maintaining normal blood Ca levels immediately post-calving [23]. As such, providing 8 to 10 g of Ca/d can lead to favorable results [24]. However, this may be hard to achieve under commercial conditions [2]. To achieve this goal, supplementing prepartum diets with Ca binders such as zeolite A, and synthetic sodium-aluminum silicate may be workable [2]. Such compounds bind minerals such as Ca, P, and Mg leading to low Ca diets through limiting Ca absorption [2]. In a survey on the effectiveness of zeolite A in optimizing the Ca status of prepartum cows, improved Ca homeostasis at calving and maintained post-calving performance were observed for the supplemented group [25]. In another study using Ca binders [26] including 90 g zeolite A/kg DM of the prepartum diet stabilized Ca concentrations at calving but decreased feed intake (6.2 ±1.3 kg vs. 12.0 ±1.4 kg; for zeolite A supplemented vs. control groups, respectively) and induced hypophosphatemia. It was concluded that zeolite A should not be used in prepartum diets at such a dosage. Supplementation of diets with phosphorous and magnesium could overcome the negative effects of zeolites in the occurrence of hypophosphatemia [27]. According to the literature, supplementing prepartum diets with aluminosilicates such as zeolite A potentially improves Ca status of cows at parturition. However, deficiency in phosphorous and magnesium states should be considered when zeolites are supplemented.

Since forages are a major part of dairy cows' rations, their chemical composition may have substantial effects on prepartum DCAD and Ca homeostasis. Alongside other sources of forage such as corn silage and grasses, alfalfa in both hay or silage forms is an important forage for the global dairy and beef industries. Alfalfa is primarily used for its high protein (18-21.5% DM, according to maturity stage) and fibre content (37-45% DM, according to maturity stage) in dairy cattle rations [28]. According to the Cumberland Valley Analytical Service's (CVAS) report, alfalfa is rich in potassium (2.53% DM) and calcium (1.53% DM), resulting in greater DCAD values [29]. It is important to note that the soil pH is critical for optimum growth of alfalfa, and a pH of about 6.7 is desirable [30]. To achieve such a pH, liming is an important practice to increase soil pH. Moreover, liming could increase alfalfa' Ca and Mg concentrations [31]. In contrast, chloride-based fertilizers may increase Cl- levels leading to lower DCAD [32]. Including alfalfa hay in prepartum diets may, thus, have undesirable effects on Ca homeostasis. However, planting conditions and use of acidifying compounds could mitigate DCAD values in alfalfa hay. Hays containing low levels of K+ (1.3% DM) could mitigate dietary DCAD and improve Ca status compared to hays with higher levels of K+(3.3% DM) [33]. To overcome the negative effects of high K+ concentrations in hays on DCAD, supplementation with anionic salts may be useful. Supplementing anionic salts to a diet containing 1.62% K decreased urinary pH [34].

In research to examine the effects of including either alfalfa hay or grass hay in prepartum diets on Ca homeostasis, no differences were observed between treatments in the incidence of hypocalcemia [29]. Thus, it was concluded that the DCAD of alfalfa is more important than its concentration of K alone [29]. Overall, alfalfa can be used in prepartum diets when its DCAD is modified by forage mineral composition or when acidogenic compounds are supplemented. In addition to alfalfa, grass species are another family of forages that can be used in dry cow diets. Because of low DCAD, grass hays are favorable forage types for prepartum cows. Feeding timothy grass to non-pregnant and non-lactating cows confirmed that low DCAD forages could improve metabolic health of dry cows [35]. In this study, blood Ca recovered more quickly (339 vs. 708 min, respectively) in low DCAD fed cows than in control cows with greater DCAD. Similarly, feeding low DCAD corn silage fertilized by chloride for dry cows resulted in significantly lower urinary pH (8.06 vs. 8.22), indicating an occurrence of mild metabolic acidosis in the low DCAD cows [36]. In addition, Ca excretion from urine was higher for the low DCAD group. Besides forage types fed to prepartum cows, evidence exists that grain type used in prepartum diets could influence the Ca status of dry cows [37]. Including wheat grain instead of barley grain in the prepartum diet resulted in reduced urinary pH at 7 d prepartum and increased Ca and glucose concentrations at 3 d postpartum. In a similar study, dry cows fed with a ground wheat (18% DM basis) containing diet showed reduced urine pH, increased prepartum feed intake, and improved Ca status and glucose levels at 7 d prepartum and 1 d postpartum [38]. Therefore, selecting optimal feed ingredients for formulating prepartum diets may be a useful strategy to manipulate mineral metabolism to improve transition cows' metabolic health.

Calcium Supplementation Postpartum

Dairy cows may be supplemented with some Ca sources without any other dietary interventions to normalize blood Ca levels immediately after calving. Oral calcium boluses and intravenous Ca injection are the two common strategies used on-farm worldwide. Calcium boluses are usually administered at two occasions postpartum including immediately after calving and 12 hours later [2]. Calcium boluses may provide 40-50 g of Ca/each bolus [2]. Oral boluses mostly consist of two Ca sources such as calcium chloride and calcium sulfate. Calcium chloride is a fast-released source whereas calcium sulfate is a slow-released source [2]. These Ca sources may enhance cows' Ca status at calving by releasing Ca continuously. It seems that the effectiveness of oral supplements is dependent on product composition, parity, feeding intervals, and production capacity of cows [39,40]. Calcium boluses ay have benefits for multiparous and high-producing cows, but it is believed that they might be detrimental for primiparous cows' reproduction [41]. Calcium boluses usefulness was also reported in multiparous cows with greater milk yield potential [41]. Injectable Ca solution is another way to prevent hypocalcemia in some farms. Administering Ca solutions intravenously may not be effective in sub-clinical cases [2]. It is likely to be effective in case of downer cows or cows with very low levels of Ca. Even, the intravenous Ca administration may negatively affect Ca homeostasis [42]. The intravenous Ca administration could induce hypocalcemia 24 hours later [42]. It is believed that rapid increase of Ca postpartum may disrupt PTH response [2]. Considering such results, oral administration of Ca may have benefits for multiparous high-producing cows.

Conclusion

Hypocalcemia is commonly experienced by dairy cows after calving following the onset of lactation. Sub-clinical hypocalcemia seems to be a threat to subsequent health and production of dairy cows. Sub-clinical hypocalcemia may be a risk factor for many metabolic and infectious diseases in early lactation. Alongside energy and protein, Ca metabolism should be addressed by the nutritional strategies managed for prepartum cows. Negative dietary DCAD is a useful approach to induce mild metabolic acidosis, a favorable condition to PTH response. Feeding low DCAD diets should be restricted to about 21 d prepartum. Very low DCAD may have detrimental effects on both dam and calf health. Oral Ca administration is another strategy to prevent hypocalcemia postpartum. It should be considered that oral supplementation is workable mainly in multiparous high-producing cows. Eventually, since Ca is an important mineral in the immune system regulation, maintaining Ca homeostasis of dairy cows should be a priority when formulating healthy commercial rations for transition cows.

Acknowledgment

Cordial thanks to Behroozi Dairy CO., (Tehran, Iran) and the National Elites Foundation (Tehran, Iran) for their supports of our studies.

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DOI: 10.26717/BJSTR.2023.50.007933

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.50.007933

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