Review

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Review: Dietary cation-anion difference to prevent hypocalcemia with emphasis on over-acidification in prepartum dairy cows

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ABSTRACT

Hypocalcemia remains a common metabolic disorder of dairy cattle; therefore, an efficient prevention is still challenging. Among the various prevention strategies for hypocalcemia is the use of anionic compounds to induce a mild metabolic acidosis during the prepartum period. Acid-base status can be readily assessed through urine pH. Accordingly, a target urine pH during the prepartum period between 6.0 and 6.8 has been recommended for Holstein cows; however, in several countries, including the US, certain nutritional strategies are still focused on benchmarking the urine pH to below 6.0. Unfortunately, over-acidification can have no advantages and/or detrimental effects on both the dam and her offspring. In this review, updated information regarding the use of anionic diets on prepartum dairy cows and the potential negative impact of such diets on both cow and calf performance are discussed. There is an urgent need for studies that will elucidate the pathophysiological mechanisms by which very acidotic diets may impact the well-being and productive efficiency of dairy cows, and the transgenerational effects of such diets on offspring performance and survival.

Implications

Anionic diets can prevent clinical hypocalcemia and reduce the negative impact of subclinical hypocalcemia. However, inducing a more severe metabolic acidification by reducing the urine pH to <6.0 in Holstein cows has proved to be not advantageous and/or more detrimental than beneficial for the dairy cow and her offspring. A rational use of anionic diets to induce a mild metabolic acidosis, reflected by a urine pH between 6.0 and 6.8, has been shown to be appropriate to control hypocalcemia in dairy cows.

Introduction

Hypocalcemia remains a common metabolic disorder of dairy cattle which may lead to reduced milk yield, poor fertility, and significant economic losses. Although the incidence of its clinical form (milk fever) has been reduced consistently during the last years (5.9% in 1996 to 2.5% in 2014) (USDA, 2018), yet, there are herds experiencing incidences over 5% (Venjakob et al., 2021). In addition, the high prevalence of subclinical hypocalcemia (**SCH**), defined as total plasma Ca (**tCa**) and ionized plasma Ca (**iCa**) concentrations of <2.15 and <1.0 mmol/L, respectively (Goff, 2018; Couto Serrenho et al., 2021c), is a concern, because 50–80% of dairy cows may be affected (Reinhardt et al., 2011; Caixeta et al., 2015; Tsiamadis et al., 2016). This metabolic condition has evolved over time. In the past, SCH occurred predominantly during the first 2 days postcalving (Reinhardt et al., 2011; Rodríguez et al., 2017). However, recently, cases of SCH have been reported beyond 2 days postpartum (Neves et al., 2018; McArt and Neves 2020), with a prevalence of 18.6% at 7–8 days postpartum in confined dairy cattle (Tsiamadis et al., 2021) and 21.7 –42.3% at 7 days postpartum in grazing dairy cows from the southern hemisphere (iCa $\leq$ 1.0 mmol/L) (Melendez et al., 2022a). Furthermore, SCH is a risk factor for other periparturient diseases (McArt et al., 2012; Overton et al., 2017; Neves et al., 2018; McArt and Neves, 2020), accounting for significant economic losses (Liang et al., 2017). Consequently, dairy farmers must look for an efficient prevention method for hypocalcemia to achieve a successful lactational performance and mitigate economic losses. Among the various prevention strategies for hypocalcemia is the use of anionic compounds (Chlorides and Sulfates) in the feed (Goff, 2014 and 2018) to alter the dietary cation- anion difference (**DCAD**) and induce a mild metabolic acidosis. However, the optimal DCAD required to avoid the development of clinical hypocalcemia has been strongly debated. The degree of metabolic acidosis can be readily assessed by measuring urine pH. A urine pH less than 6.0

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is suggestive of over-acidification. At very low blood pH, the cow immediately compensates by reducing feed intake, increasing renal proton excretion, reabsorption of potassium and bicarbonate, and rising respiratory rate, which together reduces the variability in urine pH. If blood pH drops below 7.2, the animal will become very sick and die (Goff, 2018). Accordingly, a target urine pH during the prepartum period between 6.0 and 6.8 has been suggested as appropriate for Holstein cows (Goff, 2014; Melendez and Poock, 2017), including grazing dairy herds (Melendez et al., 2021b); however, a urine pH below 6.0 (DCAD −240 mEq/kg DM) has been reported by others to improve Ca homeostasis and reduce the variability in urine pH within the herd when compared with a positive DCAD diet; however, these studies did not include an experimental group with a mild negative DCAD diet (−80 to −120 mEq/kg DM) (Glosson et al., 2020; Zhang et al., 2022). In this review, updated information regarding the use of anionic diets on prepartum dairy cows is discussed. Potential negative impact of over-acidification on the cow and her offspring is addressed. New evidence on metabolomics of urine and serum of cows fed extremely negative DCAD prepartum diets is reviewed. A comprehensive analysis of the rational use of anionic salts is provided, and a hypothesis for potential pathophysiological mechanisms of carry-over effects that can occur both in the cow and her calf due to overdosing anionic salts is proposed.

Anionic salts, dietary cation-anion difference, urine pH, and hypocalcemia

In normal blood, as the cations marginally exceed the anions, the pH is slightly alkaline (Goff, 2018). Herbivores consuming diets high in forages that are generally high in K^+ and Ca^{2+}, and relatively low in anions, such as Cl^-, SO_4^{2-}, and PO_4^{3-}, have a slightly higher blood pH than non-herbivores, which places ruminants in a state of compensated metabolic alkalosis, with no negative effects on health. In this state, the kidneys prevent alkalosis from becoming life threatening by excreting the extra K^+ into the urine. The high cation content of the urine produces the typical alkaline urine of cattle consuming forages rich in K (Goff et al., 2004; Goff, 2018). This metabolic alkalosis is further exacerbated when dairy cows are fed diets high in cations. Importantly, this state of metabolic alkalosis reduces the ability of the cow to preserve calcium homeostasis around parturition (Goff, 2014 and 2018; Wilkens et al., 2020), and the capacity to synthesize vitamin D in its active form (1,25-dihydroxyvitamin D) (Goff, 2018). Therefore, to correct the cation–anion imbalance, dietary supplementation of anions during the prepartum period has been used as an effective strategy to restore calcium homeostasis (Goff, 2014; Wilkens et al., 2020) by changing the normal alkalotic state to a mild acidotic state (Goff, 2018). This mild metabolic acidosis is related to an increased sensitivity of parathyroid hormone receptors in bone and kidney (Goff, 2014 and 2018), with a consequently enhanced mobilization of calcium reserves from bone, and calcium reabsorption from kidney and absorption from the intestine, leading to increased circulating calcium concentrations. Thus, the use of anionic compounds in prepartum diets has become a common preventative strategy for correcting hypocalcemia in dairy cows.

Several equations have been used to define the DCAD, which is expressed in milli-equivalents per kg of DM (Goff, 2018):

1. DCAD = (Na + K)/Cl
2. DCAD = (Na + K) − (Cl + S)
3. DCAD = (Na + K + 0.15 Ca + 0.15 Mg) − (Cl + 0.6 S + 0.5P)
4. DCAD = (Na + K) − (Cl + 0.6 S)

In this review, Equation (2) will be used when the DCAD level of a diet is reported. This is because it is an equation highly correlated with urine pH (Charbonneau et al., 2006).

Decreasing the DCAD during the last 3–4 weeks before parturition will prevent clinical hypocalcemia in dairy cows (Goff, 2014; Melendez and Risco, 2016; Goff, 2018). Diets high in chlorides and sulfates lead to a DCAD higher in anions (negative DCAD) and, therefore, reduce the risk of hypocalcemia (Goff, 2018). Consequently, the activity of vitamin D is improved, and enhanced bone Ca resorption takes place (Goff, 2014 and 2018). As more anions are fed, the concentration of H^+ in body fluids, including blood, is increased, and pH is reduced, which leads to metabolic acidosis. In response to these changes, the kidneys reduce the excretion of Na^+ and K^+ and reduce urine pH as compensatory mechanisms. Therefore, the evaluation of urine pH in prepartum cows fed anionic diets is a rapid and low-cost field method to screen the level of metabolic acidification (Goff, 2018; Lean et al., 2019; Wilkens et al., 2020).

Changes to dietary DCAD will affect urine pH within 48–72 h (Goff, 2014). Urine pH can be assessed using spot samples, with no need for multiple samples within a 24-hour period (Boudra et al., 2022). However, when reporting studies relating prepartum urine pH and calcium concentrations at parturition, the time of the sampling in days relative to parturition should be considered as a covariate in the models (Melendez et al., 2021a).

The optimum degree of metabolic acidosis, as reflected by urine pH, that can prevent clinical hypocalcemia is still debatable (Goff, 2014; Couto Serrenho et al., 2021a). Strategies using anionic salts are focused on reaching certain DCAD and urine pH, but doses of a specific product are not recommended, because the dose will depend on the content of cations and anions in the entire diet, therefore, a dose is not standard. One approach is to offer anionic products to reach a very negative DCAD (<−200 mEq/kg DM), targeting a urine pH below 6.0 (Glosson et al., 2020), which may lead to a potential uncompensated metabolic acidosis (very low blood pH, very low blood bicarbonate concentration, base excess close to 0 and normal $PaCO_2$) (Cunningham, 2002; Melendez et al., 2022b). In fact, the normal range of urine pH for cows consuming forages is between 8 and 8.5 (Parrah et al., 2013). A urine pH < 6.0 may suggest metabolic over-acidification which may indicate the cow is on the limits of compensatory mechanisms (Cunningham, 2002; Goff, 2018; Melendez et al., 2022b). Interestingly, cows with a urine pH close to 7.0 have been shown to experience a lower risk of developing clinical hypocalcemia (Charbonneau et al., 2006). Therefore, a urine pH for prepartum dairy cows in the range of a mild metabolic acidosis (6.0–6.8) for Holstein cows is sufficient to prevent milk fever (Charbonneau et al., 2006; Goff, 2014; Melendez and Poock, 2017).

A reduction of urine pH by 3 units (from 8.5 to 5.5) implies that the kidneys must expel 1000 times the extra H^+ produced by the body as the pH scale is logarithmic (Goff, 2018). In the meta-analysis of Charbonneau et al. (2006), it was reported that the lower the DCAD the lower the urine pH and the lower the DM intake, increasing the risk for an uncompensated metabolic acidosis. The lowest urine pH reported in this study was 5.7. In fact, cows consuming diets high in anions had an average urine pH of 5.9, but the same concentration of tCa at calving as compared with cows with a more moderated low urine pH of 6.2 (Caixeta et al., 2020); which is consistent with the results reported by Melendez and Poock (2017). Furthermore, in one of our recent studies (Melendez et al., 2021a), we reported that a diet with a DCAD of −100 mEq/kg DM induced a urine acidity near 6.5 and the concentration of blood tCa was close to 8.5 mg/dL (2.15 mmol/L), which has been defined as the cut-off concentration for SCH. This implies that cows consuming a diet that results in a urine pH between 6.0

and 7.0are sufficient to reduce the risk of clinical hypocalcemia and lessen the severity of SCH. Accordingly, prepartum cows reaching a urine pH either less than 6.0 or higher than 7.0 experienced a reduction in the concentration of plasma tCa and tended to increase the concentrations of beta hydroxy butyrate.

Whether the dietary Ca and/or the anionic strategy is more important to meet the calcium needs and maintaining acid-base balance of the cow is still unclear. In a very interesting study, using castrated male sheep as a model, the effects of low or high DCAD and dietary Ca levels on several physiological responses were studied (Freitag et al. 2021). The low DCAD groups were significantly associated with lower urine pH, higher urinary Ca excretion, and higher serum iCa concentrations; however, blood pH and bone responses did not differ significantly between groups. Based on these results, the authors concluded that is unclear from which compartment the high amounts of Ca in the urine in the low DCAD groups were originated. Interestingly, the low DCAD groups showed a higher kidney mRNA abundance for the receptors of parathyroid hormone, however, the abundance of Ca transporter mRNA was unaffected. Even though differences in serum 1,25 vitamin D concentrations, diets low in Ca did not show an upregulated compensatory mechanism of Ca transport proteins such as the apical membrane Ca channel and cytosolic Ca binding protein calbindin in renal tissue. As neither renal abundance of these transporters nor Ca excretion were influenced by dietary Ca supply, the increased urinary Ca observed with low DCAD diets represented a loss over certain threshold rather than a physiological regulated excretion mechanism of excessive Ca; thus, the authors concluded that diets with low DCAD increased the urinary excretion of Ca regardless of dietary Ca intake (Freitag et al., 2021). Interpreting these results, under practical settings, we propose that it is not worthwhile to substantially decrease DCAD because the animals will very likely excrete in urine the excessive amount of Ca mobilized from the bone and absorbed from the intestine.

Impact of very low dietary cation-anion difference on cow performance and health

We previously reported that cows reaching a urine pH < 6.0 had similar concentrations of plasma tCa at calving to cows with a urine pH greater than 6.0 (Melendez and Poock, 2017; Melendez et al., 2019); however, still there is no clear evidence of what the most effective and ideal DCAD and urine pH would be to prevent hypocalcemia without affecting the performance of the cow during the entire transition period (Goff 2018; Santos et al. 2019). There is substantial evidence that while DCAD is reduced from +300 to −200 mEq/kg DM feed, DM intake is linearly decreased, metabolic acidosis is worsened, displacement of the abomasum is more likely, fertility is reduced, and other postpartum complications occur (Charbonneau et al., 2006; Mecitoglu et al., 2016; Santos et al., 2019; Glosson et al., 2020; Vieira-Neto et al., 2021; Melendez et al., 2022b). Nevertheless, since DCAD is associated with urinary pH, but an identical DCAD may result in different urine pH (Leno et al., 2017; Glosson et al., 2020), it is recommended that to measure prepartum metabolic acidosis, the evaluation of urinary pH be used, instead of considering the value of DCAD alone.

A polynomial second-order relationship between prepartum urine pH and the risk of hypocalcemia has been reported in dairy cattle (Santos et al., 2019). Cows that had a urine pH between 5.5 and 6.5 showed a lower risk of hypocalcemia. However, the same quadratic association was demonstrated in other study, but with the highest concentration of plasma tCa between urine pH of 6.0 and 7.0 (Melendez et al., 2021a). Therefore, a more moderated urine pH achieves similar results to those of pH below 6.0, suggesting that it is not useful to target a pH less than 6.0. Likewise, the same study of Santos et al. (2019) reported that the risk of displacement of the abomasum declined from 12% in primiparous cows consuming a diet with a DCAD – 200 mEq/kg DM (corresponding to a urine pH 5.7) to 6% in cows consuming a diet with a DCAD of +200 mEq/kg DM (corresponding to a urine pH 8.0). Remarkably, in another investigation, an association between the occurrence of displaced abomasum, blood, and urine pH, and serum tCa concentration was reported. Dairy cows that developed a left displacement of the abomasum had a lower prepartum urine pH (6.11 ± 0.2 vs 6.65 ± 0.1) and blood pH (7.27 ± 0.01 vs 7.32 ± 0.01) than contemporary cows without the digestive condition, respectively. However, the concentration of serum iCa was similar between both groups (Mecitoglu et al., 2016). In addition, in two recent studies using the same data set (Lopera et al., 2018; Vieira-Neto et al., 2021), where prepartum cows receiving a diet with a DCAD + 110 mEq/kg DM were compared with cows consuming a diet with a DCAD of −70 and another group consuming a diet with a DCAD of −180 mEq/kg DM, the results revealed that the DM intake of the −180 DCAD was 1.1 kg/d lower than the −70 mEq/kg DM, and the DM intake of the −70 DCAD was 0.8 kg/d lower than the control diet. The urine pH was approximately 6.5 and 5.5 in cows fed a DCAD of −70 and −180 mEq/kg DM, respectively. In addition, blood pH decreased linearly when DCAD decreased from −70 and −180 mEq/kg DM. Furthermore, cows fed a diet with −180 mEq/kg DM produced less milk at first milking than cows fed a diet with −70 mEq/kg DM; however, plasma tCa and blood iCa concentrations and the incidence of periparturient diseases were similar between both groups. Moreover, cows fed a more acidogenic diet had a reduced release of insulin after a glucose challenge and an increased level of hormone-sensitive lipase, which tended to increase the release of fatty acids after an insulin challenge. These changes were not explained at the mRNA level, as the expression of genes related to gluconeogenesis in adipose and liver tissues were not altered by the DCAD level. Vieira-Neto et al. (2021) concluded that diets inducing a more aggressive acidosis (DCAD −180) might alter the release and tissue responsiveness to insulin, which consequently shifts the protein profile in adipose tissue to favor lipolysis over lipogenesis. In addition, this higher lipolysis might also be the result of the lower DM intake of cows consuming a diet with a more negative DCAD.

The adverse impacts of excessive negative DCAD have also been corroborated by a recent study (Beck et al., 2022) where a diet with a DCAD of −154 mEq/kg DM resulted in urine pH < 6.0 from 20 days before expected parturition until calving, similar serum tCa concentration at calving, higher urine Ca excretion, higher prepartum serum NEFA (450 μEq/L) and lower milk fat % when compared to a group of cows fed a prepartum diet with a moderately positive DCAD (+89 mEq/kg DM).

In another recent study, diets with a negative prepartum DCAD increased serum tCa and iCa during the postpartum period, with concentrations that are above the cut-off value for SCH (8.5 mg/dl tCa; 4 mg/dl iCa) when compared with a diet with positive DCAD. For the group with a DCAD of −180 mEq/kg DM, postpartum tCa and iCa were 9.0 and 4.60 mg/dL, respectively, and for the group of −100 mEq/kg DM were 8.56 and 4.43 mg/dl (no subclinical hypocalcemia), respectively. The control group (DCAD 0 mEq/kg DM) had a postpartum tCa and iCa of 8.0 and 4.08 mg/dl (subclinical hypocalcemia), respectively. In addition, there were no differences in milk yield or milk fat, between both negative DCAD diets and the control group (Hassanien et al., 2022), suggesting that there is no advantage in overfeeding anionic salts (DCAD −180 mEq/kg DM) to achieve the same results as with a −100 mEq/kg DM diet.

Little is known of the effects of DCAD diets that drop urine pH below 6.0 on the overall health condition of cows and their calves.

Table 1
Least square means, and SEM for urine pH and blood metabolites in Early Dry and Prepartum Holstein cows (n = 15) and *P*-values for period, parity and BCS effect (Melendez et al., 2022b).

Variable	Early dry DCAD +250	Prepartum DCAD −220	SEM	Period effect (*P*-value)	Parity effect (*P*-value)	BCS effect (*P*-value)
Urine pH	8.18	5.33	0.20	<0.0001	0.13	0.25
Blood pH	7.50	7.36	0.048	<0.0001	0.79	0.86
Base Excess (mmol/L)	2.46	−7.79	1.75	<0.0001	0.65	0.93
Lactate (mmol/L)	0.99	1.49	0.55	0.021	0.90	0.29
HCO_3 (mmol/L)	25.65	17.45	1.51	<0.0001	0.43	0.68
sO_2 (%)	68.73	52.00	16.3	0.01	0.93	0.71
TCO_2 (mmol/L)	26.59	18.39	1.63	<0.0001	0.37	0.59
pCO_2 (mm Hg)	32.62	30.68	4.39	0.23	0.57	0.66
pO_2 (mm Hg)	37.51	29.85	18.52	0.26	0.54	0.87

Abbreviations: BCS = body condition score; DCAD = dietary cation-anion difference; TCO_2 = total carbon dioxide; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; sO_2 = % oxygen saturation; HCO_3 = bicarbonate.

In a study conducted in Chile and Argentina (Melendez et al., 2021a), 60 prepartum Holstein cows were selected at random to obtain a urine sample to assess its pH. Additionally, a blood sample was collected within 6 hours of parturition to measure plasma metabolite concentrations. A polynomial curvilinear association between urine pH and tCa concentration was detected. Plasma concentration of tCa was greater in cows having a urine pH between 6.0 and 7.0, whereas the calcaemia decreased when urine pH was either below 6.0 or above 7.0. These findings are comparable to other reports (Charbonneau et al., 2006; Ramos-Nieves et al., 2009; Wu et al., 2014). Lower tCa plasma concentrations in cows with urine pH below 6.0 might be explained due to the reduction in feed intake occurring in cows fed very low negative DCAD diets, as reported by others (Charbonneau et al., 2006; Zimpel et al., 2018; Lean et al., 2019; Caixeta et al., 2020; Glosson et al., 2020). In addition, a curvilinear relationship between urine pH and the concentration of blood BHBA was also observed (Melendez et al., 2021a), where cows having either a urine pH below 6.5 or above 7.5 showed greater blood BHBA concentrations, which could also be supported by the lower feed intake of cows consuming diets extremely high in anions. In fact, a recent study (Zhang et al., 2022), investigating the metabolic effect of a diet with a DCAD of − 241 mEq/kg DM that led to a urine pH below 6.0, showed that the prepartum cows had lower DM intake than controls and had higher concentration of plasma NEFA (>0.3 mmol/L). The same high levels of NEFA (450 μEq/L) in cows consuming a prepartum diet with a DCAD of −154 mEq/kg DM were reported in a study conducted at Oklahoma State University (Beck et al., 2022). Although the cows consuming the very low DCAD diet may compensate for the metabolic acidosis within the first 24 hours postpartum, the higher NEFAs prepartum deserve more attention because these levels have been consistently related to lower lactational performance. Prepartum cows with NEFA concentrations >0.3 mmol/L are more susceptible to experience more postpartum diseases, have lower fertility and produce less milk during the subsequent lactation (Ospina et al., 2010a and 2010b).

Contrary to a more negative DCAD, a Canadian study (Couto Serrenho et al., 2021a) that used a mild negative DCAD (−100 mEq/kg DM) showed a mean urine pH of 6.3 ± 0.6, improving milk yield in multiparous cows, but not in primiparous cows. Furthermore, the mild acidogenic diet improved fertility only in multiparous cows by increasing the odds of pregnancy at first artificial insemination 1.53 times (95% CI = 1.097–2.21). Similarly, the mild negative DCAD diet decreased the odds of culling in multiparous cows (OR = 0.58, 95% CI: 0.41–0.82) (Couto Serrenho et al., 2021a). In an accompanying publication, multiparous cows fed the mild negative DCAD diet had a greater blood tCa concentration during the first 4 days postpartum than multiparous cows consuming a control diet. In addition, the proportion of cows with SCH (tCa ≤ 2.14 mmol/L) was lower in the moderate negative DCAD diet than the control diet, with no differences detected in primiparous cows (Couto Serrenho et al., 2021b). Interestingly, the authors detected interactions between treatment and body condition score (BCS) at enrollment for milk fever in multiparous cows. Obese multiparous cows (BCS ≥ 3.75) treated with a mild negative DCAD had a reduced incidence of milk fever, from 13 to 2%. In addition, treated cows had a lower incidence of displacement of the abomasum (1.7%) than control cows (3.6%). Since these studies were carried out in several Canadian commercial farms, the authors concluded that commercial farms offering prepartum diets with a mild DCAD of −108 mEq/kg DM to target an acid urine with a pH ranging from 6.0 to 6.5 in multiparous dairy cows improved their postpartum health, calcium status, milk production and reproductive efficiency.

Based on the studies reviewed above, we suggest that lowering DCAD beyond −100 mEq/kg DM and/or lowering urine pH below 6.0 does not improve the lactational cow performance and on the contrary may adversely affect health parameters such as feed intake, insulin responsiveness, and fat mobilization.

Impact of very low dietary cation-anion difference on calf health

A more severe metabolic acidosis may also have negative consequences for calf well-being (Hasegawa et al., 2019). Cows with lower urine pH (<6.0) experienced a greater proportion of stillbirths (13.6%) than cows with alkaline urine (4.4%) (Melendez et al., 2021a). Additionally, a more acidogenic diet was demonstrated to shorten the length of gestation of dairy cows by 2 days (Lopera et al., 2018), a result that deserves further consideration. Certainly, insulin resistance, rise of ketone bodies in blood, an exacerbated metabolic acidosis, along with a reduction in DM intake during the peripartum period are strong metabolic disturbances that may induce stress during the final stages of pregnancy that may potentially impact the calf survival (Mills et al., 1986; Ling et al., 2018; van Gastelen et al., 2021). Furthermore, plasma cortisol concentrations were higher in pregnant ewes fed anionic salts (DCAD −88.9 mEq/kg DM) when compared with positive DCAD diets, especially 1 day before parturition (Espino et al., 2005). This large cortisol response may also trigger off a calving difficulty with additional negative consequences for the offspring (e.g., stillbirths) and cow performance (Arnott et al., 2012). However, the underlying pathophysiological mechanisms by which very low DCAD diets directly impact the animal performance remain largely understudied. A more severe metabolic acidosis is stressful enough for the cow to affect its fetus in uterus and has a higher incidence of stillbirths when exposed to potential uncom-

Table 2
Studies reporting adverse impacts of very low negative DCAD diets on health and performance of cows.

Study	DCAD[1]	Blood Acid-Base prepartum and metabolites			Urine pH	Major findings	Reference
Comparison of 3 prepartum DCAD diets		tCa (mg/dl)	iCa	PTH (pg/ml)		Same energy corrected milk yield in both negative DCAD. Normal tCa/iCa in both negative DCAD. Trend for lower calf BW in −180 DCAD	Hassanien et al. (2022)
	0	8.03	4.08	62.4	8.02 ± 0.06		
	−100	8.56	4.43	50.6	7.02 ± 0.05		
	−180	9.05	4.60	34.7	5.93 ± 0.03		
Comparison positive vs 2 negative DCAD with 2 sources of vit D		tCa (mg/dl)		NEFA (meq/L)		Higher NEFA and lower tCa with lower urine pH. Similar milk yield.	Beck et al. (2022)
	+89	7.82		202	7.72 ± 0.1		
	−154	8.86		304	6.34 ± 0.1		
	−154	8.38		450	6.16 ± 0.1		
Comparison (+) vs very low (−) DCAD	+ 60 −240	↓ [glucose] and ↑ [NEFA] than control group during prepartum			(−) DCAD pH < 6.0	Negative DCAD ↓ DMI	Zhang et al. (2022)
Comparison of cows with high and low urine pH	+250 −220	blood pH: 7.50 & 7.36; base excess: 2.46 & −7.79 mmol/L; lactate: 0.99 & 1.49 mmol/L, respectively			+250: 8.18 −220: 5.33	Metabolomics negative DCAD: ↑ [NEAA] and [glucogenic AA] in plasma and ↓ levels in urine, and ↓ PC aa and PC ae moieties in plasma and urine	Melendez et al. (2022b)
Comparison of cows with high and low urine pH	−109 −128	↓ [tCa], ↑ [BHB] with urine pH < 6.0 and > 7.0 (quadratic function)			11 cows (pH < 6.0) 55 cows (pH ≥ 6.0)	Stillbirths (SBs) Cows with pH < 6.0 = 13.4% SB Cows with pH 6.0–7.0 = 8.8% SB Cows with pH > 7.0 = 4.4% SB	Melendez et al. (2021a)
Comparison of positive and negative DCAD in nulliparous cows	+200 −50 −150	Base excess: 4.43, 2.49, and 0.06, respectively			+200: 8.22 −50: 6.67 −150: 5.41	[tCa] at calving similar among 3 groups. −150 DCAD more RFM, metritis, mastitis, and DA than the rest of the groups	Zimpel et al. (2021)
Moderate negative DCAD vs Positive DCAD	+110 −100	N/A			8.1 ± 0.4 6.3 ± 0.6 respectively	Milk fever incidence Obese + 100 DCAD 13% Obese −110 DCAD 1.8% Normal + 100 DCAD 4.6% Normal −110 DCAD 2.2%	Couto Serrenho et al. (2021a and 2021b)
Comparison positive vs very low negative DCAD	+60 −240	[tCa] = 2.0 mmol/L at calving.			Cows with negative DCAD pH < 6.0	Very Low DCAD: trend ↓ colostrum. More milk fever and same DA cases than controls. ↓ DMI than control group.	Glosson et al. (2020)
Moderate negative DCAD vs Control group	+265 −94	↑ [tCa] than control. (2.15 mmol/L).			Negative DCAD 6.12	Only 30% SCH. Similar DMI	Jahani-Moghadam et al. (2020)
Moderate negative DCAD + 3 mg calcidiol vs positive DCAD	+140 −124	[tCa] = 2.181 ± 0.02 mM NEFA prepartum < 0.3 mmol/L			Not reported	Mild negative DCAD ↓ % milk fever (23.1 vs 0%) and SCH. ↑ EC milk yield	Martinez et al. (2018a and 2018b)
Moderate and very low DCAD for 21 days (S) or 42 days (L)	−70 −180	Blood pH −70S = 7.42, −180S = 7.385, −70L = 7.41 −180L = 7.381 Base Excess −70S = 1.75 −180S = − 2.26, −70L = 1.07 −180L = − 1.43			−70S: 6.46 −180S:5.62 −70L: 6.48 −180L:5.56	↓ DMI in −180S and L vs −70S and L. Same [tCa] postpartum for 4 treatment groups. Same incidence of milk fever (3.5%) between −70S and −180S	Lopera et al. (2018)
Three DCAD treatments	+192 −114 −113	Blood pH 7.43, 7.42, 7.41 Base Excess 1.45, −0.20, −0.95, respectively			+192 = 7.92 −114 = 5.66 −113 = 5.54	DMI significant linear reduction with lower blood pH.	Zimpel et al. (2018)
Moderate and very low DCAD for 21 days (S) or 42 days (L)	−70 −180	At birth, calves from−180 (pH = 7.33 ± 0.02; pCO_2 = 53.0 ± 2.4 mmHg; HCO_3 = 27.6 ± 0.7 mmol/L)−70 (pH = 7.28 ± 0.02; pCO_2 = 59.3 ± 2.4 mmHg; HCO_3 = 27.8 ± 0.7 mmol/L).			Not reported	62 d old calf BW −70S 80.7 kg, −180S 82.3 kg, −70L 78.4 kg, −180L 75.1 kg. 3 days shorter gestation length for cows fed negative DCAD for 42 d	Collazos et al. (2017)
Moderate vs Very Low DCAD	−113 −121	Blood [BHB] −113 = 6.07 mg/dl; −121 = 8.98 mg/dl			−113 = 6.52 −121 = 5.93	Same milk yield & [tCa] at calving	DeGroot et al. (2010)

[1] DCAD = dietary cation-anion difference, meq/kg DM [Na + K] – [Cl-S]; SCH = subclinical hypocalcemia; NEFAs = non-esterified fatty acids; BHB = beta hydroxy butyrate; DA = displacement of abomasum; RFMs = retained fetal membranes; EC = energy corrected; tCa = total calcium; iCa = ionized calcium; AAs = amino acids; NEAAs = non-essential amino acids; PTH = parathyroid hormone; N/A = no-applicable; pCO_2 = partial pressure of carbon dioxide; DMI = DM intake; PC aa = phosphatidylcholine containing diacyl moieties; PC ae = phosphatidyl choline containing acyl-alkyl moieties.

pensated metabolic acidosis reflected by low prepartum urine pH (<6.0) and low DM intake. As an example, in the study of Hassanien et al. (2022), there was a tendency ($P = 0.16$) for better quality colostrum in a group fed a diet with a DCAD of −180 mEq/kg DM than the group of −100 mEq/kg DM; however, there was also a tendency ($P = 0.16$) for a lower calf birth weight (40.1 ± 0.44 kg) in the group of −180 mEq/kg DM than the group of −100 mEq/kg DM (41.5 ± 0.44 kg). As the sample size was only 16 cows per group, the study was likely underpowered to detect statistical differences in the calf birth weight. Therefore, there may potentially be a detrimental effect of diets with a very low negative DCAD (less than −100 to −120 mEq/kg DM) on calf birth weight and subsequent health.

Very low dietary cation-anion difference, acid-base status and metabolomics

Previous research on metabolic responses to dietary negative DCAD traditionally focused on the usual metabolites (e.g., glucose, triglycerides, NEFA). We recently provided insights into the blood acid-base parameters and metabolomics of plasma, and urine in prepartum Holstein cows fed an anionic diet with very low DCAD (Melendez et al., 2022b). Those cows consuming an amount of anionic salts sufficient to lower urine pH to 4.96–5.74 had a very low base excess in blood, indicative of a severe metabolic acidosis. In addition, they had a higher concentration of blood lactate than cows consuming a positive DCAD diet (Table 1). We noted that cows on the negative DCAD diet had lower urine concentrations of aromatic amino acids, lysine, histidine, and threonine, and lower essential amino acids and glucogenic amino acids, whereas, they had greater circulating concentrations of total non-essential and glucogenic amino acids. Interestingly, the dietary anionic salts exerted marked effects on a number of plasma glycerophospholipids. Further studies are necessary to assess whether circulating and/or urine metabolomic profiles are predictive of cows susceptible to metabolic acidosis, and whether these indices revert to normal after the restoration of normal acid-base status. In Table 2, studies reporting adverse impacts of very low negative DCAD diets on cow/calf performance and health are summarized.

Conclusions

With the current knowledge, producers and nutritionists could protect against milk fever and reduce the negative impact of SCH and improve cattle lactational performance with dietary supplementation of anionic salts. However, such a nutritional intervention should be tempered by secondary carry-over effects that excessive anionic salts may impose on the physiological adaptations in the cow and calf. A moderate metabolic state with a urine pH between 6.0 and 7.0 seems to be sufficient to control and prevent clinical hypocalcemia and reduce the incidence of SCH. A more severe acidotic state has been demonstrated to be no advantageous and/or more detrimental than beneficial for the cow, and likely her offspring. There is an urgent need for studies that elucidate the pathophysiological mechanisms by which very low negative DCAD diets impact the health and productivity of dairy cows, and the transgenerational effects of such diets on offspring health and performance.

Ethical approval

Not applicable.

Data and model availability statement

Not applicable. No data in an official repository.

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Declaration of interest

None.

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