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Impact of Lowering Dietary Cation-Anion Difference in Nonlactating Dairy Cows: A Meta-Analysis

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ABSTRACT

A meta-analysis of previous studies was performed to clarify the response of prepartum dairy cows to lowering dietary cation-anion difference (DCAD) and to compare different equations that have been proposed to calculate DCAD. Twenty-two published studies containing 75 treatment groups met criteria for inclusion in the meta-analysis. Five different equations used to calculate DCAD were compared for their association with clinical milk fever and urinary pH. The DCAD equation (Na + K) – (Cl + 0.6 S) was the most highly associated with clinical milk fever (R^2 = 0.44) and urinary pH (R^2 = 0.85). Lowering DCAD reduced clinical milk fever but also reduced DM intake. Lowered DCAD was associated with reduced urinary pH, blood bicarbonate, and blood CO_2, suggesting a metabolic acidosis with respiratory compensation. Blood pH was very slightly lowered by lowered DCAD. Lowering DCAD increased ionized Ca in blood before and at calving. The model predicted that lowering DCAD from +300 to 0 mEq/kg reduced risk for clinical milk fever from 16.4 to 3.2%, reduced urinary pH from about 8.1 to 7.0, and reduced DM intake by 11.3%.

Key words: nonlactating dairy cow, dietary cation-anion difference, milk fever, urinary pH

INTRODUCTION

Hypocalcemia is an important problem in dairy cattle around parturition. It occurs when cows are unable to compensate for the dramatic increase in Ca needed for colostrum production at calving. The most dramatic form of hypocalcemia is clinical milk fever, which can be fatal. Surviving cows have increased risk for retained fetal placenta, displaced abomasums, and mastitis (Curtis et al., 1983; Gröhn et al., 1989) and decreased milk yield (Block, 1984) compared with cows without clinical milk fever. Subclinical milk fever, a milder form of hypocalcemia, may also be detrimental and may put cows at higher risk for developing subsequent metabolic disorders (Huber et al., 1981; Oetzel et al., 1988).

Dishington (1975) first reported that feeding a mixture of chloride and sulfate salts before calving could dramatically reduce the incidence of clinical milk fever. Numerous studies that followed have confirmed that lowering DCAD before calving reduces the risk for clinical and subclinical milk fever. Lowered DCAD has been associated with a compensated metabolic acidosis, which is evidenced by reduced plasma bicarbonate (Goff and Horst, 1997; Joyce et al., 1997; Pehrson et al., 1999), lower urinary pH (Wang and Beede, 1992a; Eppard et al., 1996; Moore et al., 2000), and higher urinary net acid excretion (Wang and Beede, 1992b; Van Mosel et al., 1993; Vagnoni and Oetzel, 1998). Blood pH is compensated in part by bone accepting hydrogen ion in exchange for Ca (Lemann et al., 2003). Calcium excreted in the urine in response to acidosis may be retained when Ca demand increases. However, Schonewille et al. (1999) reported that the amount of Ca retained by the cow from urinary Ca loss was not sufficient to account for all of the extra Ca mobilized during an EDTA challenge. Other mechanisms are also apparently involved, such as increased tissue receptivity to parathyroid hormone during acidosis (Goff et al., 1991). Improved parathyroid hormone receptiveness results in increased production of active vitamin D, which in turn enhances bone resorption and intestinal absorption of Ca (Gaynor et al., 1989; Goff et al., 1991).

Numerous equations have been published for the calculation of DCAD in dairy cattle diets. The first published equation (Ender et al., 1971) was (Na + K) – (Cl + S). Other DCAD equations were proposed later to account for the contributions of dietary ions that are not completely bioavailable. These longer equations were (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.6 S + 0.5 P) (Horst and Goff, 1997), (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.2 S + 0.3 P) (Horst and Goff, 1997), and (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.6 S + 0.5 P) (National Research Council, 2001). A fifth equation, (Na + K) – (Cl + 0.6 S), was recently proposed by Goff et al. (2004). This equation appeared to be the most accurate

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Table 1. List of previously published studies meeting requirements for inclusion in the meta-analysis, number of treatment groups within each study, and dietary cation-anion difference (DCAD) values for each treatment group

Study	Treatment groups	DCAD1[1] of treatment groups
Block, 1984	2	331; –129
Delaquis and Block, 1995	2	473; 328
Eppard et al., 1996	2	195; –132
Gant et al., 1998	3	530; –6; –6
Goff and Horst, 1997	7	461; 436; 407; 221; 202; –53; –98
Goff and Horst, 1998	2	313; –181
Joyce et al., 1997	3	351; 303; –70
Kume et al., 2001	2	186; 178
Leclerc and Block, 1989	4	392; 120; 110; 60
Moore et al., 2000	6	142; 142; 0; 0; –148; –148
Oetzel and Barmore, 1993	6	315; 116; 114; 113; 109; 109
Oetzel et al., 1988	4	190; 187; –75; –76
Pehrson et al., 1999	3	172; –48; –163
Roche et al., 2003	2	508; –20
Roche et al., 2002	4	530; 469; 452; 438
Tucker et al., 1992	4	94; 94; –34; –34
Vagnoni and Oetzel, 1998	4	201; –41; –57; –61
van Dijk and Lourens, 2001	4	135; 135; –118; –118
Van Mosel et al., 1993	4	530; 530; –6; –6
Wang and Beede, 1990	3	269; 210; 147
Wang and Beede, 1992a	2	69; –428
Wang and Beede, 1992b	2	–289; –302

[1]DCAD1 = (Na + K) – (Cl + S), mEq/kg of dietary DM.

in predicting blood pH and standard base excess from dietary mineral composition (Goff et al., 2004).

To date, different DCAD equations have only been evaluated within individual studies. Combining data from many published studies into a meta-analysis allows comparison of these equations across a variety of experimental conditions. A meta-analysis also provides additional statistical power that could detect significant differences in outcomes that are not statistically different in individual studies.

A meta-analysis of milk fever studies in dairy cows has been published (Oetzel, 1991). However, only a few of the studies included in that analysis reported dietary mineral composition determined by wet chemistry analysis, and many of the mineral values used to calculate DCAD from the studies included in this analysis were estimated from tables of feed ingredient composition. And since then, many additional studies evaluating the relationship between DCAD and numerous outcomes have been published. Statistical methods to perform meta-analysis have also improved (St-Pierre, 2001).

The objectives of this study were 1) to compare the different DCAD equations for their impact on clinical milk fever and urinary pH and 2) to evaluate the impact of lowering DCAD on clinical milk fever, urinary pH, DMI, measures of acid-base balance, and blood Ca concentrations.

MATERIALS AND METHODS

Study Selection

A meta-analysis on the effect of lowering DCAD in nonlactating dairy cows was conducted by pooling and analyzing data from previous studies. To be included in the meta-analysis, studies needed to meet all the following criteria: 1) peer-reviewed publication in print before 2004; 2) English or French language for at least the abstract of the publication; 3) nonlactating dairy cows used as the experimental animals; 4) dietary amounts of Na, K, Cl, and S reported; 5) use of wet chemistry procedures for dietary mineral analysis; 6) dietary analysis results within the range of reasonable expectations for dairy cattle diets; 7) outcomes that included clinical milk fever, urinary pH, DMI, measures of acid-base status, or blood Ca; and 8) no vitamin D treatments administered.

Twenty-two published studies for 75 different treatment groups met all the inclusion criteria (Table 1). Treatment groups excluded due to mineral analyses outside the range of reasonable expectations included the anionic treatment in Goff et al. (1991) and the 2 treatment groups in experiment 2 from Goff and Horst (1998) due to low reported Na content (0.04 and 0.03% Na, respectively, DM basis). Also excluded were all treatment groups in Oetzel et al. (1991) due to high reported S values in the basal diet (>0.47%, DM basis).

Table 2. Descriptive statistics of outcomes from previous studies meeting requirements for inclusion in the meta-analysis

Outcome	n	Mean	SD	Maximum	Minimum
DCAD[1] equation					
DCAD1,[2] mEq/kg	75	123.6	222.3	530.4	–427.9
DCAD2,[3] mEq/kg	57	328.6	187.6	834.8	–56.6
DCAD3,[4] mEq/kg	57	310.0	176.1	723.3	–49.8
DCAD4,[5] mEq/kg	57	179.0	182.9	631.1	–221.4
DCAD5,[6] mEq/kg	75	205.8	208.1	612.7	–284.2
Clinical milk fever, %	33	18.2	21.7	80.0	0.0
Urinary pH	48	7.49	0.94	8.68	5.70
DM intake, kg/d	44	10.8	2.2	16.0	5.7
Blood outcomes					
HCO_3^-,[7] m*M*	28	25.0	1.99	27.8	20.5
pCO_2,[8] mmHg	19	39.4	4.5	46.6	32.8
pH	35	7.41	0.03	7.47	7.31
Total Ca nonlactating, mg/dL	24	8.76	0.97	9.88	6.56
Ionized Ca nonlactating, mg/dL	20	4.71	0.28	4.96	3.89
Total Ca at calving, mg/dL	22	7.46	1.08	8.80	4.82
Ionized Ca at calving, mg/dL	17	4.17	0.39	4.76	3.51

[1]DCAD = Dietary cation-anion difference, DM basis.
[2]DCAD1 = (Na + K) – (Cl + S).
[3]DCAD2 = (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.6 S + 0.5 P).
[4]DCAD3 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.2 S + 0.3 P).
[5]DCAD4 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.6 S + 0.5 P).
[6]DCAD5 = (Na + K)– (Cl + 0.6 S).
[7]HCO_3^- = Adjusted blood bicarbonate.
[8]pCO_2 = Blood CO_2 partial pressure.

The DCAD for the diet fed each treatment group was calculated from the reported mineral levels; calculated DCAD values reported in each study were not recorded. This was done to eliminate minor variations in the methods used to calculate DCAD in the different studies. Five different equations were used to calculate DCAD for each treatment group:

DCAD1 (mEq/kg) = (Na + K) – (Cl + S)
DCAD2 (mEq/kg) = (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.6 S + 0.5 P)
DCAD3 (mEq/kg) = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.2 S + 0.3 P)
DCAD4 (mEq/kg) = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.6 S + 0.5 P), and
DCAD5 (meq/kg) = (Na + K) – (Cl + 0.6 S).

Because 3 equations included Ca, Mg, and P values in the calculation of DCAD, the reported dietary content of those minerals was recorded when available. Studies did not have to report values for those 3 minerals to be included in the analysis; however, they could not be included in the analysis for the DCAD equations that included these minerals. The valence of P was assumed to be 1.8, which represents the normal distribution of monohydrogen and dihydrogen forms of P in body tissues (Oetzel, 1993).

Data Recording from Selected Studies

Group mean values for clinical milk fever, urinary pH, DMI, blood pH, blood HCO_3^-, blood CO_2 partial pressure (**pCO_2**), and total or ionized blood Ca around calving were added to the analysis if they were reported for the study. Group means for DMI were recorded but only if cows were offered ad libitum feed intake. Many studies reported additional outcomes that could have been of interest; however, only the outcomes listed here were reported by a sufficient number of treatment groups to allow for valid statistical evaluation.

Data reported in differing units of measure were transformed to the same units. When a study did not report all possible outcomes, missing variables were considered as missing data. Studies with results reported for both primiparous and multiparous cows were split into separate treatment groups for those 2 categories.

Statistical Analyses

Effects of DCAD on Study Outcomes. Mixed model procedures from SAS (SAS Institute, 1997) were used to evaluate the effect of lowering DCAD5 on study outcomes. The unit of measure was the mean value from treatment groups. Data were weighted by the number of cows in each study to help counteract variation between

Table 3. Effects of 5 different DCAD[1] equations on clinical milk fever and urinary pH; data derived from treatment group means in previous studies

Outcome, equation	n	Intercept	SE	*P*	Slope	SE	*P*	Residual SE	R^2	*P*
Arcsin Sqrt CMF (%)[2]										
DCAD1[3]	25	0.2496	0.07743	0.01	0.000724	0.000242	<0.01	0.2027	0.40	<0.01
DCAD2[3]	25	0.08740	0.1183	0.48	0.000628	0.000223	0.01	0.1908	0.40	<0.01
DCAD3[3]	25	0.07214	0.1136	0.55	0.000777	0.000256	<0.01	0.1876	0.44	<0.01
DCAD4[3]	25	0.1807	0.09625	0.10	0.000713	0.000250	0.01	0.1930	0.40	0.03
DCAD5[3]	25	0.1802	0.08524	0.07	0.000790	0.002530	<0.01	0.1970	0.44	<0.01
LOGIT (urinary pH/9)[4]										
DCAD1[5]	43	1.5293	0.08665	<0.01	0.002886	0.000328	<0.01	0.5205	0.78	<0.01
DCAD2[5]	43	0.8307	0.1619	<0.01	0.002666	0.000389	<0.01	0.9158	0.58	<0.01
DCAD3[5]	43	0.7887	0.1533	<0.01	0.003203	0.000405	<0.01	0.5963	0.69	<0.01
DCAD4[5]	43	1.1986	0.09760	<0.01	0.003074	0.000356	<0.01	0.6001	0.71	<0.01
DCAD5[5]	43	1.2574	0.1070	<0.01	0.003100	0.000358	<0.01	0.5218	0.78	<0.01

[1]DCAD = Dietary cation-anion difference, mEq/kg of dietary DM; DCAD equations are: DCAD1 = (Na + K) – (Cl + S); DCAD2 = (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.6 S + 0.5 P); DCAD3 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.2 S + 0.3 P); DCAD4 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.6 S + 0.5 P); DCAD5 = (Na + K) – (Cl + 0.6 S).

[2]Arcsin Sqrt CMF = $\sin^{-1}$ (√ clinical milk fever, %).

[3]Equation to calculate clinical milk fever (untransformed basis) is as follows: clinical milk fever, % = $\{\sin [\text{intercept}_i + (\text{slope}_i \cdot \text{DCAD}_i)]\}^2$, where i represents the DCAD equation used.

[4]LOGIT (urinary pH/9) = log {(urinary pH / 9) / [1 – (urinary pH/9)]}.

[5]Equation to calculate urinary pH (untransformed basis) is as follows: urinary pH = $\{[e^{\text{intercept}_i + (\text{slope}_i \times \text{DCAD}_i)}] \times [1 + e^{\text{intercept}_i + (\text{slope}_i \times \text{DCAD}_i)}]^{-1}\} \times 9$, where i represents the DCAD equation used.

experiments (St-Pierre, 2001). The study was entered as a random effect. It was not possible to include slope and intercept by study as random effects, as suggested by St-Pierre (2001), because there were not enough different treatment groups in most of the studies.

Preliminary analyses were conducted to determine viability of linear models, and final models were then determined by logistic regression. Clinical milk fever data were transformed (arc sine square root) to meet homogeneity of variance criteria. Urinary pH data were also transformed (logit) to best represent the nonlinear relationship between DCAD and urinary pH.

Comparison of DCAD Equations. The 5 different DCAD equations were analyzed for their relationship to clinical milk fever and urinary pH with the approach described above. Treatment groups for this analysis were limited to studies that reported data for all minerals (including Ca, Mg, and P) and for which all 5 equations could be calculated. For proper graphic representation of statistical results in 2 dimensions, the Y observation was adjusted to take into account the random effect of study. The coefficient of multiple regression (R^2) calculations also used the adjusted Y observation (St-Pierre, 2001).

RESULTS AND DISCUSSION

Descriptive statistics of outcomes included in the analysis are presented in Table 2. All studies had to

Table 4. Effect of dietary cation-anion difference (DCAD5)[1] on DM intake and blood outcomes; data derived from treatment group means in previous studies

Outcome	n	Intercept	SE	*P*	Slope	SE	*P*	Residual SE	R^2	*P*
DM intake, kg/d	42	10.1029	0.5588	<0.01	0.004288	0.000700	<0.01	0.9383	0.66	<0.01
Blood outcomes										
HCO_3^-, m*M*	28	23.7115	0.6380	<0.01	0.007457	0.001137	<0.01	2.6870	0.80	<0.01
pCO_2, mmHg	19	38.9591	1.8947	<0.01	0.006169	0.001802	<0.01	5.0919	0.64	<0.01
pH	35	7.3989	0.008917	<0.01	0.000061	0.000023	0.01	0.001722	0.30	<0.01
tCa[2], mg/dL	24	8.6629	0.2793	<0.01	0.000859	0.000702	0.24	1.2875	0.10	0.11
iCa[3], mg/dL	20	4.7728	0.07964	<0.01	–0.00073	0.000212	<0.01	0.07665	0.64	<0.01
tCa at calving, mg/dL	22	8.0711	0.3929	<0.01	–0.00260	0.000909	0.01	1.4546	0.60	<0.01
iCa at calving, mg/dL	17	4.3964	0.1345	<0.01	–0.00159	0.000240	<0.01	0.05813	0.84	<0.01

[1]DCAD5 (mEq/kg) = (Na + K) – (Cl + 0.6 S).

[2]tCa = Total Ca in blood.

[3]iCa = Ionized Ca in blood.

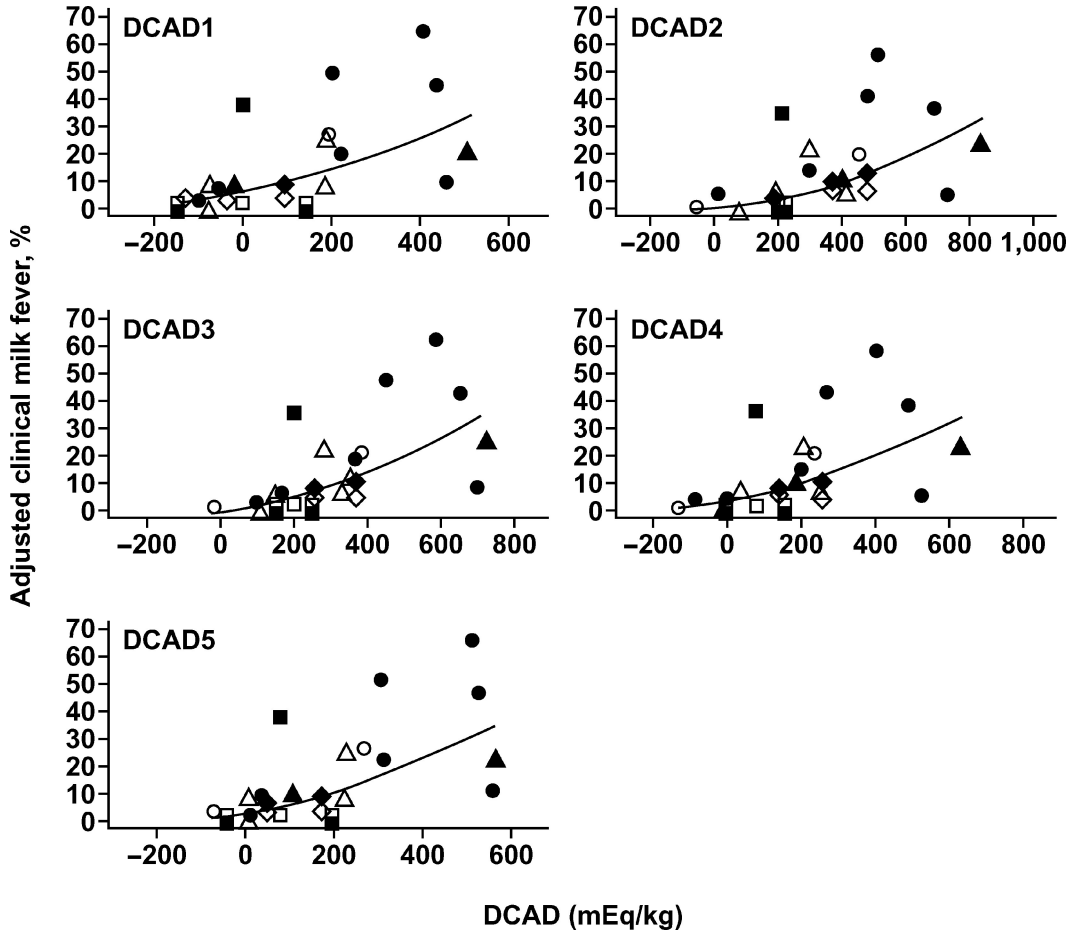

Figure 1. Effect of dietary cation-anion difference (DCAD) on clinical milk fever. Five different DCAD equations are plotted: DCAD1 = (Na + K) – (Cl + S); DCAD2 = (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.60 S + 0.50 P); DCAD3 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.20 S + 0.30 P); DCAD4 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.60 S + 0.50 P); and DCAD5 = (Na + K) – (Cl + 0.6 S). Data are group treatment means from previous studies: ○ = Eppard et al. (1996); ● = Goff and Horst (1997); □ = Moore et al. (2000; primiparous); ■ = Moore et al. (2000; multiparous); △ = Oetzel et al. (1988); ▲ = Roche et al. (2003); ◇ = Tucker et al. (1992; primiparous); ◆ = Tucker et al. (1992; multiparous).

report dietary Na, K, Cl, and S to be included; therefore, DCAD1 and DCAD5 equations were available for all 75 treatment groups. Fifty-seven treatment groups were from studies also reporting Ca, Mg, and P values; DCAD2, DCAD3, and DCAD4 could be calculated for those treatment groups. Urinary pH results were reported for 48 treatment groups, and clinical milk fever was reported for 33 treatment groups. Maximum and minimum values are reported to demonstrate the wide range of independent and dependent variables represented in the studies.

Comparisons of DCAD Equations

All 5 DCAD equations evaluated were significantly and negatively associated with clinical milk fever (Table 3 and Figure 1). The DCAD3 and DCAD5 equations had the strongest association with clinical milk fever ($R^2 = 0.44$). There was no advantage to using the longer equation (DCAD3) over the shorter equation (DCAD5) for predicting clinical milk fever. The other equations, DCAD1, DCAD2, and DCAD4, had slightly lower R^2 values.

The effectiveness of lowering DCAD in reducing clinical milk fever was highly relevant biologically as well as being statistically significant. For example, reducing DCAD5 from +300 to 0 mEq/kg of dietary DM (as would be accomplished by adding 3 equivalents of chlorides to the diet of a cow consuming 10 kg of DM/d) reduced the modeled incidence of clinical milk fever from 16.4 to 3.2%.

All 5 DCAD equations were also significantly and negatively associated with urinary pH (Table 3). The R^2 values ranged from 0.58 to 0.78 (Table 3) with DCAD1 and DCAD5 having the highest correlation.

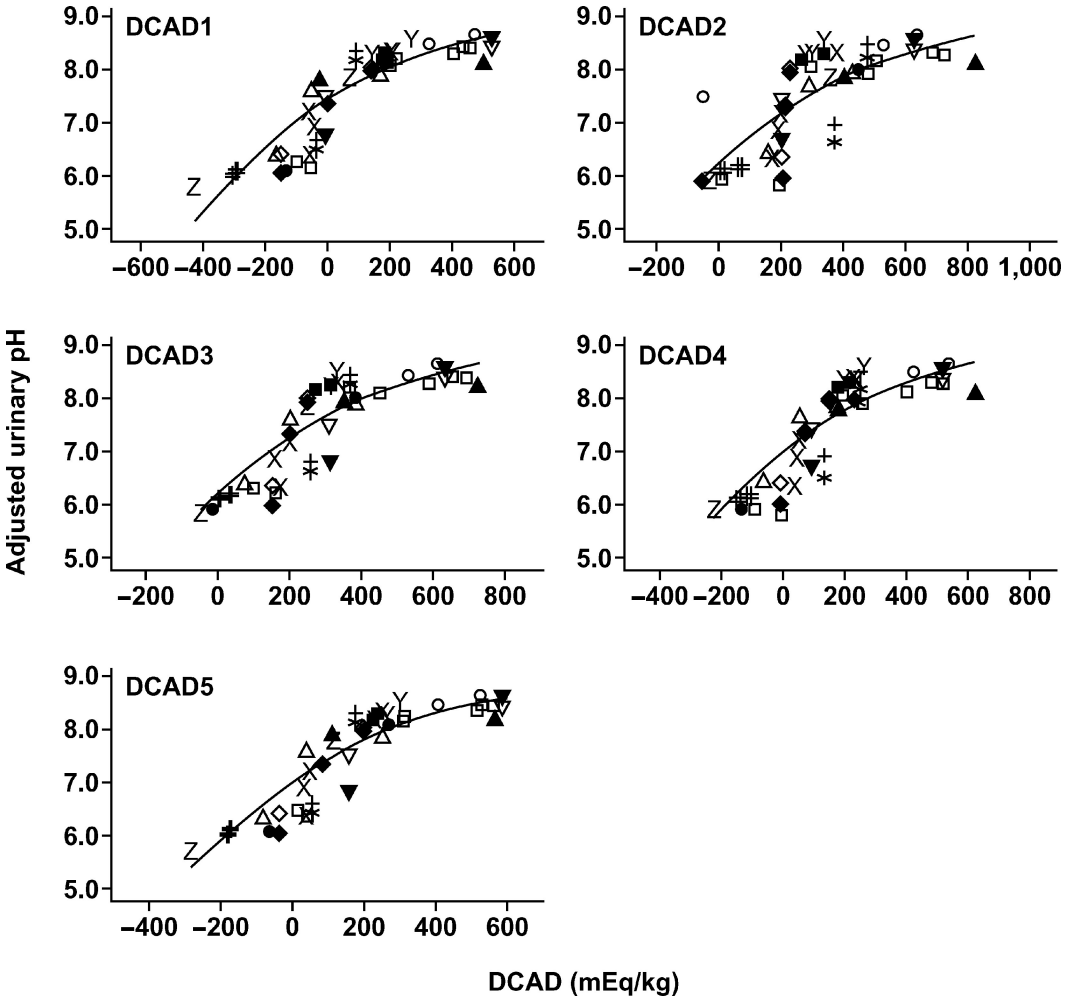

Figure 2. Effect of dietary cation-anion difference (DCAD) on urinary pH. Five different DCAD equations are plotted: DCAD1 = (Na + K) – (Cl + S); DCAD2 = (Na + K + 0.38 Ca + 0.30 Mg) – (Cl + 0.60 S + 0.50 P); DCAD3 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.20 S + 0.30 P); DCAD4 = (Na + K + 0.15 Ca + 0.15 Mg) – (Cl + 0.60 S + 0.50 P); and DCAD5 = (Na + K) – (Cl + 0.6 S). Data are group treatment means from previous studies: ○ = Delaquis and Block (1995); ● = Eppard et al. (1996); □ = Goff and Horst (1997); ■ = Kume et al. (2001); △ = Moore et al. (2000; primiparous); ▲ = Moore et al. (2000; multiparous); ◇ = Pehrson et al. (1999); ◆ = Roche et al. (2003); ∗ = Tucker et al. (1992; primiparous); + = Tucker et al. (1992; multiparous); **x** = Vagnoni and Oetzel (1998); ▽ = Van Mosel et al. (1993; primiparous); ▼ = Van Mosel et al. (1993; multiparous); **Y** = Wang and Beede (1990); **Z** = Wang and Beede (1992a); # = Wang and Beede (1992b).

Lowered DCAD resulted in a nonlinear decrease in urinary pH (Figure 2).

The effect of lowering DCAD on urinary pH was also biologically relevant as well as statistically significant. For example, reducing DCAD5 from +300 to 0 mEq/kg of dietary DM (as described above) reduced urinary pH by from 8.09 to 7.01. These results support the practical value of using urinary pH to monitor prefresh cows that are fed reduced DCAD diets (Goff et al., 2004).

Results from the urinary pH models suggest that urinary pH does not have to be decreased below about 7.0 to reasonably prevent clinical milk fever. For example, a DCAD5 of 0 mEq/kg would result in a group average urinary pH of 7.01 and a very low incidence of clinical milk fever (3.2%). The recommendation to reduce urinary pH to between 6.0 and 7.0 for milk fever prevention (Jardon, 1995) may be lower than necessary on the lower end of the range. For example, creating a urinary pH of 6.2 would require a very low DCAD5 of –150 mEq/kg and would reduce the modeled incidence of clinical milk fever to 0.4%. This could represent excessive acidification for only a modest benefit in milk fever prevention (about 2.8 percentage units) compared with reducing urinary pH only to about 7.0.

The longer DCAD equations, which incorporated other minerals besides Na, K, Cl, and S, showed no advantage over the shorter equations. And the best equation that included S (DCAD5) assigned it only 60%

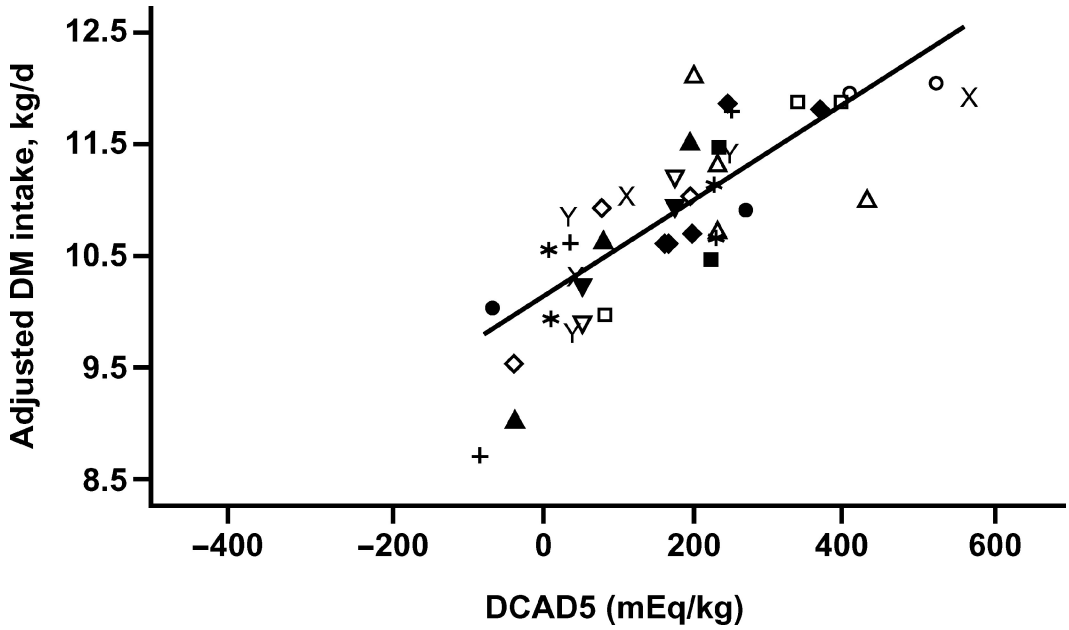

Figure 3. Effect of dietary cation-anion difference (DCAD5) [(Na + K)- (Cl + 0.6 S)] on DM intake in nonlactating cows. Data are group treatment means from previous studies: ○ = Delaquis and Block (1995); ● = Eppard et al. (1996); □ = Joyce et al. (1997); ■ = Kume et al. (2001); △ = Leclerc and Block (1989); ▲ = Moore et al. (2000; primiparous); ◇ = Moore et al. (2000; multiparous); ◆ = Oetzel and Barmore (1993); ∗ = Oetzel et al. (1988); + = Pehrson et al. (1999); **x** = Roche et al. (2003); ∗ = Tucker et al. (1992; primiparous); + = Tucker et al. (1992; multiparous); **Y** = Vagnoni and Oetzel (1998).

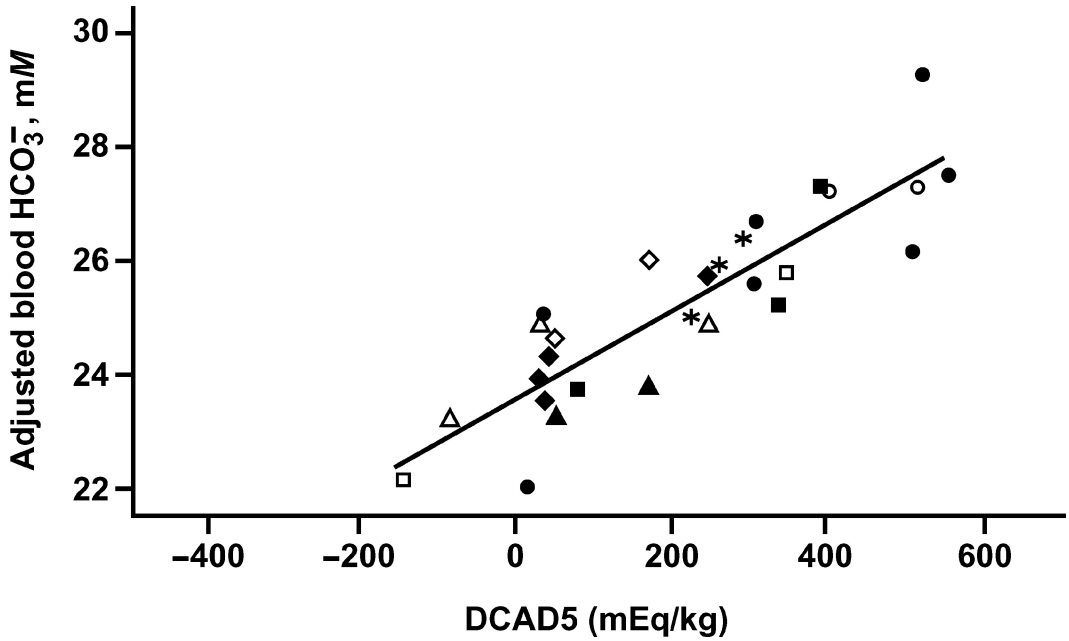

Figure 4. Effect of dietary cation-anion difference (DCAD5) [(Na + K) – (Cl + 0.6 S)] on blood HCO_3^-. Data are group treatment means from previous studies: ○ = Delaquis and Block (1995); ● = Goff and Horst (1997); □ = Goff and Horst (1998); ■ = Joyce et al. (1997); △ = Pehrson et al. (1999); ▲ = Tucker et al. (1992; primiparous); ◇ = Tucker et al. (1992; multiparous); ◆ = Vagnoni and Oetzel (1998); ∗ = Wang and Beede (1990).

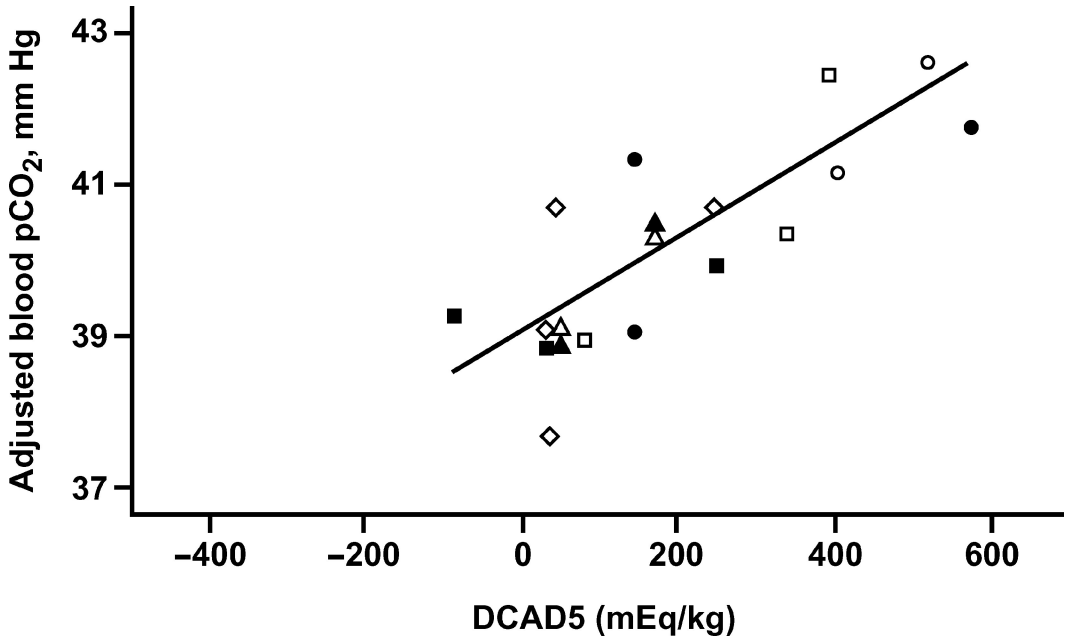

Figure 5. Effect of dietary cation-anion difference (DCAD5) [(Na + K) – (Cl + 0.6 S)] on blood partial pressure of CO_2 (pCO_2). Data are group treatment means from previous studies: ○ = Delaquis and Block (1995); ● = Gant et al. (1998); □ = Joyce et al. (1997); ■ = Pehrson et al. (1999); △ = Tucker et al. (1992; primiparous); ▲ = Tucker et al. (1992; multiparous); ◇ = Vagnoni and Oetzel (1998).

of the value of Na, K, or Cl. These findings support the theory that monovalent ions in the diet are the most bioavailable and therefore exert the strongest influence on acid-base balance (Goff et al., 2004).

The DCAD1 equation is widely used in applied dairy nutrition and is well correlated to urinary pH and clinical milk fever. However, the DCAD5 equation was equally correlated to clinical milk fever and had a much higher correlation to urinary pH. This result is in agreement with findings of a recent study (Goff et al., 2004), which was not included in the current study because it was published after the meta-analysis was completed.

Responses to DCAD

Because the DCAD5 equation had the highest correlations to clinical milk fever and urinary pH, this equation was chosen to evaluate the effect of DCAD on the other outcomes recorded. The magnitude of changes in outcomes was based on a reduction in DCAD5 from 300 to 0 mEq/kg.

Decreased DCAD5 in nonlactating cows significantly decreased DMI (Table 4 and Figure 3). The magnitude of reduction in DMI change with lowered DCAD was substantial, equaling a loss of 1.3 kg of DM/d (11.3%) for lowering DCAD5 by 300 mEq/kg. Most individual studies did not report significant reductions in DMI due to lowered DCAD; however, this meta-analysis of previous results clearly demonstrated a DMI reduction. Theories proposed to explain DMI reduction when DCAD is lowered include lack of palatability of the anion sources (Oetzel and Barmore, 1993) and some discomfort created by the acidosis itself (Vagnoni and Oetzel, 1998). However, neither of those theories has been specifically evaluated.

The benefits of milk fever prevention from lowering DCAD must be weighed against problems that could arise from reduced DMI before calving, and over-acidification in an attempt to prevent milk fever should be avoided. This could be especially important for prepartum heifers. Moore et al. (2000) reported that feeding supplemental anions significantly reduced energy balance and increased liver triglyceride content in prepartum heifers. However, cows fed anionic salts did not experience significantly reduced energy balance or liver triglyceride content. They suggested that anionic salts should not be fed to prepartum heifers and that energy content of prepartum diets should be adjusted to account for reduced DM intake when anionic salts are supplemented.

Lowered DCAD resulted in a metabolic acidosis (significantly lowered adjusted blood HCO_3^- and lowered urinary pH) that was not fully compensated (significantly lowered blood pH). Decrease of DCAD5 by 300 mEq/kg changed blood HCO_3^- substantially (–2.2 m*M* or –8.6%; Table 4 and Figure 4). These results were expected and were previously reported as significant

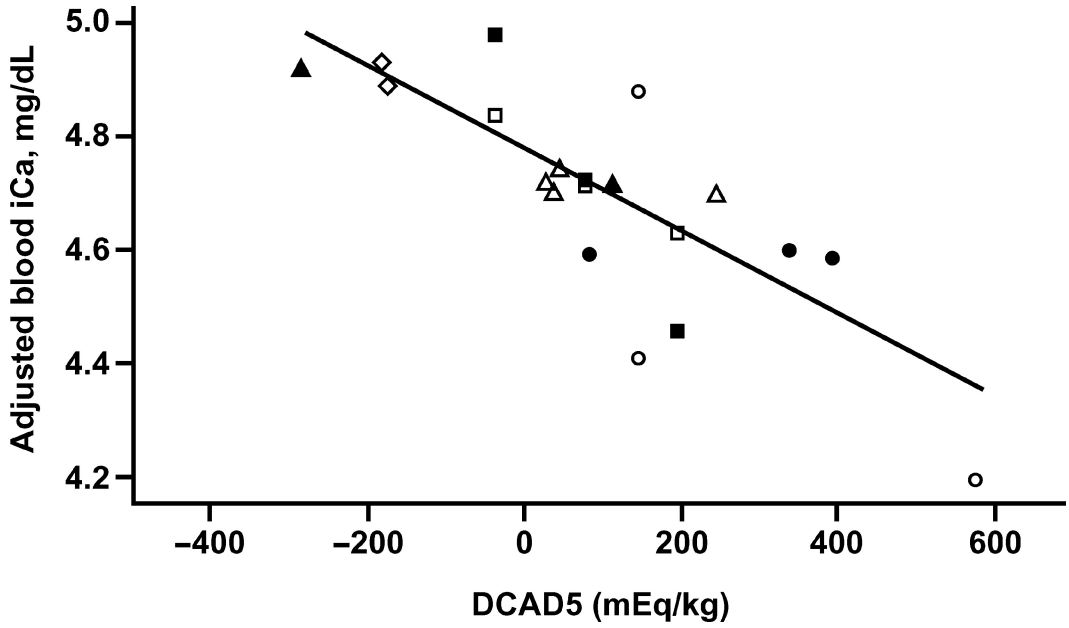

Figure 6. Effect of dietary cation-anion difference (DCAD5) [(Na + K) – (Cl + 0.6 S)] on blood ionized Ca (iCa) in nonlactating dairy cows. Data are group treatment means from previous studies: ○ = Gant et al. (1998); ● = Joyce et al. (1997); □ = Moore et al. (2000; primiparous); ■ = Moore et al. (2000; multiparous); △ = Vagnoni and Oetzel (1998); ▲ = Wang and Beede (1992a); ◇ = Wang and Beede (1992b).

findings in individual studies. Blood pH has not been reported to be significantly affected by lowering DCAD in individual studies; however, the meta-analysis demonstrated a significant and negative effect of lowering DCAD5 on blood pH (Table 4). The reduction was biologically small (–0.018 pH units, or –0.25%) and resulted in blood pH values that remained within the expected normal range of about 7.35 to 7.45 (Constable, 1999). However, small changes in blood pH could have large effects on parathyroid hormone receptivity and ultimately on the risk for clinical milk fever (Goff et al., 1991).

Lowering DCAD also significantly reduced blood pCO_2 (Table 4 and Figure 5). The magnitude of the decrease was –1.9 mmHg (–4.5 %) in response to lowering DCAD by 300 mEq/kg. This finding suggests that there is a respiratory component to dairy cow responses to diet-induced acidosis. Respiratory mechanisms provide a more rapid response to acidosis than do metabolic changes (Stewart, 1983). Changes in pCO_2 in response to lowering DCAD5 did not result in values outside the expected normal range of 35 to 45 mmHg (Constable, 1999). The finding of a significant reduction in pCO2 with lowering DCAD has not been reported in most individual studies but was evident in the meta-analysis.

Lowering DCAD in nonlactating cows did not significantly affect blood total Ca ($P = 0.11$, Table 4) in nonlactating cows but did significantly increase blood ionized Ca (Table 4 and Figure 6). The magnitude of the increase in blood ionized Ca was not great (0.22 mg/dL or 4.8%) in response to lowering DCAD5 by 300 mEq/kg. This difference was not significant in many of the individual studies that reported blood ionized Ca results for nonlactating cows. The finding of a significant ionized Ca response without a total Ca response suggests that the acidosis induced by lowering DCAD does slightly shift the proportion of Ca in the ionized fraction. This is the expected response to acidosis (Wang and Beede, 1992a).

Decreased DCAD before calving significantly increased both total and ionized blood Ca (Table 4 and Figures 7 and 8). The magnitude of the change in ionized Ca at calving (0.48 mg/dL or 12.2%) in response to lowered DCAD5 by 300 mEq/kg was much greater than the change in ionized Ca in nonlactating cows. This finding was expected, because calving and the onset of lactation creates a great challenge to Ca homeostasis. The magnitude of the increase in total Ca at calving (0.78 mg/dL or 10.7%) was very similar to the ionized Ca response. This finding suggests that shifting more Ca to the ionized fraction is probably a minor explanation for increased blood Ca concentrations at calving when DCAD is lowered.

Lowering of DCAD before calving may also decrease risk for other parturient diseases, such as retained fetal membranes or displaced abomasum. Clinical milk fever itself increases the risk for these diseases (Curtis et al., 1983), and hypocalcemia, even if subclinical, may be an

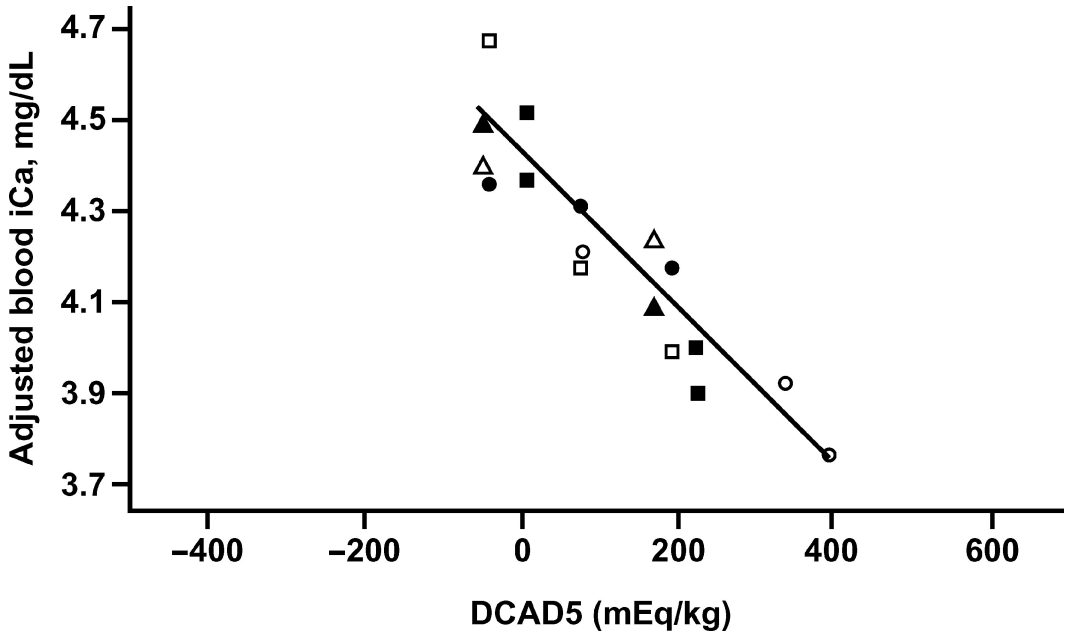

Figure 7. Effect of dietary cation-anion difference (DCAD5) [(Na + K) – (Cl + 0.6 S)] on blood ionized Ca (iCa) in dairy cows after calving. Data are group treatment means from previous studies: ○ = Joyce et al. (1997); ● = Moore et al. (2000; primiparous); □ = Moore et al. (2000; multiparous); ■ = Oetzel et al. (1988); △ = van Dijk and Lourens (2001; primiparous); ▲ = van Dijk and Lourens (2001; multiparous).

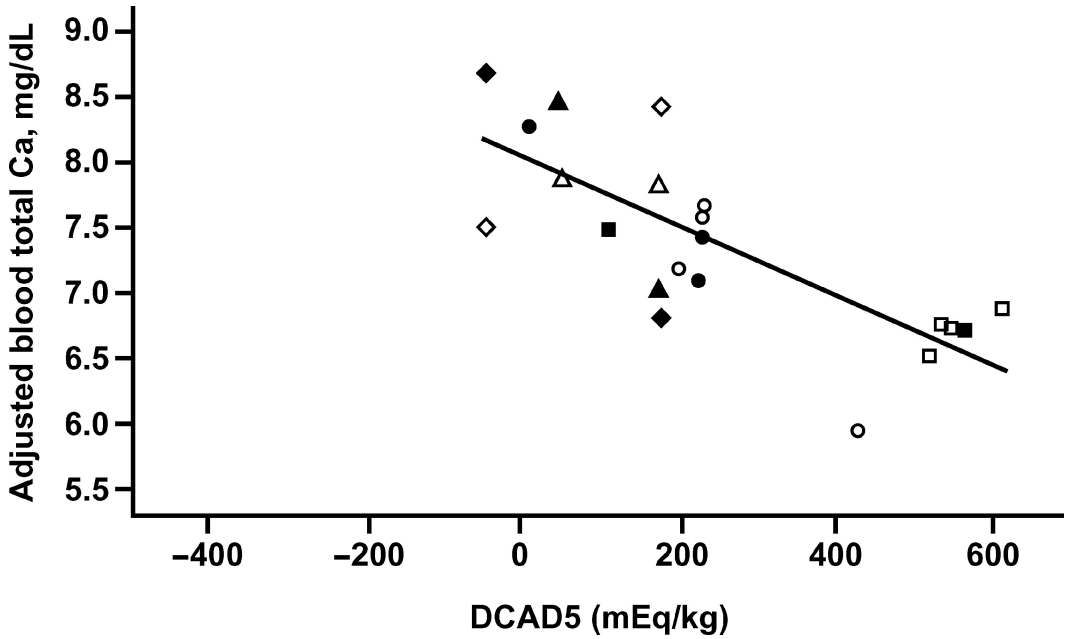

Figure 8. Effect of dietary cation-anion difference (DCAD5) [(Na + K) – (Cl + 0.6 S)] on blood total Ca in dairy cows after calving. Data are group treatment means from previous studies: ○ = Leclerc and Block (1989); ● = Oetzel et al. (1988); □ = Roche et al. (2002); ■ = Roche et al. (2003); △ = Tucker et al. (1992; primiparous); ▲ = Tucker et al. (1992; multiparous); ◇ = van Dijk and Lourens (2001; primiparous); ◆ = van Dijk and Lourens (2001; multiparous).

important risk factor for other diseases (Oetzel, 1996). Few of the individual studies included in this meta-analysis reported the incidence of other diseases so they could not be evaluated.

CONCLUSIONS

Results from this meta-analysis confirm the effectiveness of lowering DCAD to decrease urinary pH and clinical milk fever. The DCAD5 equation [(Na + K) – (Cl + 0.6 S)] was the most highly correlated to clinical milk fever incidence and urinary pH. Lowering of DCAD in nonlactating cows resulted in a metabolic acidosis that was not fully compensated. Cows responded to acidosis via both metabolic and respiratory mechanisms. The meta-analysis confirmed that lowering of DCAD increases Ca available to prepartum dairy cows before and at calving and reduces the risk for clinical milk fever. Group mean urinary pH of about 7.0 appears to be a reasonable goal when feeding low DCAD diets. Acidification beyond urinary pH of about 7.0 could further decrease DMI without much additional benefit toward milk fever prevention.

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