African Journal of Biotechnology Vol. 9(47), pp. 7976-7988, 22 November, 2010
Available online at http://www.academicjournals.org/AJB
DOI: 10.5897/AJB09.1927
ISSN 1684–5315 © 2010 Academic Journals

Review

Dietary cation anion difference: Impact on productive and reproductive performance in animal agriculture

Muhammad Sharif*, Muhammad Aasif Shahzad, Mahr-un-Nisa and Muhammad Sarwar

Institute of Animal Nutrition and Feed Technology, University of Agriculture, Faisalabad, Pakistan.

Accepted 15 March, 2010

Various nutritional tools have been used to improve the productive and reproductive performance of animals, among which difference between certain minerals, called dietary cation anion difference (DCAD) plays a pivotal role. Low or negative DCAD diets reduce blood pH and HCO_3^- and animal becomes acidotic. This improves Ca absorption from the intestinal tract. It also induces mobilization of Ca from bones which improves Ca status of the animal, thus preventing the occurrence of milk fever at the time of parturition. This may increase milk production and health in subsequent lactation. However, animals fed high DCAD diets before parturition may suffer from milk fever. Milk fever affected animals have increased plasma cortisol level that causes immunosuppression at calving. It is also positively associated with other problems like retained placenta, mastitis and udder edema. On the other hand, feeding high DCAD diet results in increased ruminal pH which is pre-requisite for optimal microbial activity as well as improving the feed intake of the animal. Improved dry matter intake (DMI) is positively correlated with milk yield by providing precursors for various milk constituents. High DCAD diet results in increased milk fat percent due to shifting of ruminal volatile fatty acid production towards acetic acid and butyric acid. It also improves energy balance of the animal which causes increased blood flow towards ovaries and increased progesterone synthesis and follicular development due to positive association between energy balance and postpartum ovulation, which leads to improved reproductive performance of the animal. While feeding low DCAD diet reduces feed intake which causes negative energy balance in early lactating animals that lessens conception rate and increases services per conception. In conclusion, feeding low DCAD diets prepartum prevents the occurrence of milk fever via improving Ca status while feeding high DCAD diets results in improved productive and reproductive performance in lactating animals.

Key words: Feed intake, milk yield, reproductive performance, hypocalcaemia, dietary cation anion difference.

INTRODUCTION

Formulation of a ration according to physiological stage of animals plays a pivotal role in optimizing their productive and reproductive performance. By providing balanced ration, milk production can be improved. At the same time, it helps in reducing reproductive disorders (Osmanu, 1979). This is especially important one month before parturition and during early lactation. Just after parturition, there is excessive loss of calcium (Ca) from the plasma pool to the formation of colostrum which must be replenished by increasing intestinal Ca absorption and bone Ca resorption. If the loss of Ca is not replaced, animal may suffer from milk fever. Animals with milk fever may result in depressed feed intake and decreased milk production (Block, 1984). Milk fever may also lead to other disorders like dystocia, retained placenta, ketosis, metritis, displaced abomasum and mastitis (Gröhn et al., 1989; Wilson and Stevenson, 1998) which affect the health of animal. During early lactation, animal requirement for nutrients increases manifolds due to increased milk

*Correspondence author. E-mail: drsharifuaf@yahoo.com.

Abbreviations: **DCAD**, Dietary cation anion difference; **VFA**, volatile fatty acids, **NDF**, neutral detergent fiber; **ADF**, acid detergent fiber; **OM**, organic matter; **CP**, crude protein; **IGF**-I, insuline like growth factor; **DMI**, dry matter intake; **PTH**, parathyroid hormone.

synthesis. Reduced feed intake during this period may lead to negative energy balance which affects animal productive and reproductive performance (Stevenson and Britt, 1980; Butler et al., 1981). Concentrate feeding is practiced to meet the nutrient requirement which decreases ruminal pH due to increased volatile fatty acids (VFA) production. It also depresses biosynthetic activities in mammary glands aimed to synthesize milk fat due to decreased acetate: propionate (Doreau et al., 1999; Bauman and Griinari, 2003).

Various nutritional tools have been used to combat these problems. Among these, manipulation of minerals in ration formulation is significant. Minerals are necessary to carry out various biological functions in animal's body. These may carry positive (cations) or negative (anions) charge. The difference between certain cations (Na^+ and K^+) and anions (Cl^- and S^{--}), in milliequivalents, is usually referred to as dietary cation anion difference (DCAD). The concept of DCAD is based upon the maintenance of desirable acid base status. Dishington (1975) and Mongin (1981) were the first who used the concept of DCAD in livestock and poultry, respectively. Since then, it has been used in prepartum and postpartum animals due to its beneficial effect.

The strong cations and anions determine the body fluid pH (Stewart, 1981) and are used to calculate DCAD which is given as:

Cations – Anions = DCAD in milliequivalent per kilogram of dry matter (mEq/kg of DM).

Where

mEq / 100 g = [(milligrams) (Valence) / (g atomic weight)]

The equations below are mainly used to calculate DCAD

$(Na^+ + K^+) - (Cl^- + S^{--})$ = mEq/100 gm of DM………… (Tucker et al., 1992)

$2(Na^+ + K^+) - (Cl^-)$ = mEq / 100 gm of DM………………. (Mongin, 1981)

The DACD may also be calculated by using the dietary percent of respective minerals (on DM (dry matter) basis) with the following equation (Olson, 1991; West, 1993; Oetzel, 1993):

DCAD = [(Na% / 0.023) + (K%/0.039)] – [Cl % / 0.0355) +(S% /0.016)] mEq/100 g DM

Various salts have been used to attain the desired level of DCAD. For example, $NaHCO_3$, $KHCO_3$ and Na_2CO_3 are used to increase the DCAD level while calcium chloride ($CaCl_2$) and magnesium sulphate ($MgSO_4$) are used to decrease DCAD level. Sodium (Na), potassium (K) and chloride (Cl^-) are believed to be completely absorbed, where as sulfate is absorbed up to 60% in early, mid and late lactation as well as during the dry period (Delaquis and Block, 1995a, b, c).

DCAD affects acid base status and Ca metabolism of the animal. Low DCAD diet results in decreased blood and urine pH and depressed bicarbonate (HCO_3^-) concentration (Block, 1994). The decrease in blood HCO_3^- and urine pH works as a compensatory mechanism. It also increases blood H^+ concentration which induces slight acidosis that improves Ca absorption (Moore et al., 2000). Slight metabolic acid situation due to feeding low DCAD diets in prepartum animals has been reported to stimulate parathyroid hormone (PTH) production which accelerates absorption of Ca^{++} from intestine. This plays key role in reducing the occurrence of hypocalcemia (Block, 1984; Fredeen et al., 1988b; Espino et al., 2003). Cows recovered from milk fever have 8 times more chances of ketosis, mastitis and uterine prolapse compared to non-milk fever cows (Curtis et al., 1983). On the other hand, feeding high DCAD diet during early lactation improves dry matter intake (DMI) (Tucker et al., 1988; Delaquis and Block, 1995b) and milk production (Hu and Murphy, 2004) by improving ruminal pH that favors optimum microbial activity (Roche et al., 2005). It can also improve the reproductive performance of the animal by improving the energy status.

Keeping in view the significance of DCAD on acid base status and animal productive and reproductive performance, the current attempt has been made to review and present the available possible information in lactating and gestating animals.

NUTRIENT INTAKE

Hu and Murphy (2004) conducted a meta-analysis and observed a linear increase in DMI with increasing DCAD levels in the diet. They reported a positive correlation between DCAD and DMI. Similarly, findings were reported by Oetzel and Barmore (1993) who observed an increasing trend in DMI as DCAD was increased from –109 to +313 mEq/kg DM. Hu et al. (2007) also supported these findings. Increased DMI at high DCAD diets might be due to increased rumen pH (Tucker et al., 1988; Sharif et al., 2009; Sharif et al., 2010) that makes the ruminal environment alkaline, which is pre-requisite for optimum ruminal microbial activity. Delaquis and Block (1995b) observed 15.2 and 16.2 kg/d DMI in early lactating cows fed 55.5 and 258.1 mEq/kg DCAD diets, respectively. Likewise, during mid lactation, DMI increased from 15.6 to 17.0 kg/d as DCAD level was increased from 140.2 to 372.7mEq/kg DCAD. They also recorded increased water consumption at high DCAD level in dairy cows during early and mid lactation. Similar findings were reported by West et al. (1992) who observed increased feed intake when DCAD level was increased from 12 to 46 mEq/100 g DM in heat stressed cows. However, Jackson et al.

(1992) reported a quadratic response in feed consumption in dairy calves fed diets containing DCAD 0, 21, 37 and 52 mEq/100 g DM. Minimum (3.79 kg/d) and maximum (4.41 kg/d) feed intake was observed in calves fed 0 and 37 mEq/100 g of DM, respectively, while a significant reduction (3.93 kg/d) was observed at 52 mEq/kg DM. This decrease in DMI with increasing DCAD might be attributed to the wide range (0 to 52 mEq/100 g of DM) of DCAD levels used in their study.

Spanghero (2004) reported a decrease in DMI by animals fed low DCAD diets. Similar findings have also been reported by Tucker et al. (1992) who determined the DCAD effect in heifers and mature cows. They observed decreased DMI in cows fed low DCAD diet. The plausible explanation for this decrease in DMI might be due to un-palatability of anionic salts (Goff et al., 1988; Shahzad et al., 2008a, b) used to reduce the DCAD level. Goff et al. (1991) also reported that feeding negative DCAD diets reduced feed consumption due to poor palatability of salts. Another plausible explanation might be that low DCAD induces slight metabolic acidosis, which reduces DMI (Block, 1994). These findings are consistent with other workers (Yen et al., 1981; Escobosa et al., 1984; Tucker et al., 1988; Sharif et al., 2009) who reported decreased DMI in cows with low DCAD diet when $CaCl_2$ was used to attain the desired low DCAD level. Biological studies executed under different environment to know response of DCAD on ruminant animal performance reflects that the DCAD can enhance nutrients intake due to its favourable influence on rumen dynamics and blood chemistry. However, the extent of nutrients intake varies depending on the level of DCAD, diet composition, animal productive potential and environment.

NUTRIENT DIGESTION

Influence of varying DCAD diets on nutrient digestibility was investigated by Delaquis and Block (1995a). They studied the effect of DCAD (481, 327 meq/kg of DM) on neutral detergent fiber (NDF) and acid detergent fiber (ADF) digestibilities in dry cows and reported that DCAD had non-significant effect on ADF and NDF digestibilities. In another study, Delaquis and Block (1995b) reported that during lactation period, DM digestibility was slightly higher in cows fed +55 compared to +375 mEq/kg DCAD diets, respectively. However, the difference was statistically non-significant. The NDF digestibility also remained unaltered by DCAD alteration. This might be attributed to the speculation that DCAD had no significant effect on ruminal fermentation pattern in lactating cows (Tucker et al., 1991).

Keeping in view the significance of sodium bicarbonate ($NaHCO_3$) as cationic salt in DCAD studies, several researchers used this salt to divert the electrical composition of diet towards more alkaline to counteract the slight ruminal acidosis which animals may experience when fed on nutrient rich diet. Canale and Stokes (1988) observed the influence of $NaHCO_3$ supplementation on forage source and nutrient digestibility and reported that apparent dry matter digestibility of the corn silage based diet was greater than hay crop silage. The $NaHCO_3$ supplementation improved the digestibility of NDF in both diets but did not significantly affect the digestion of other nutrients. These findings were consistent with other workers (DePeters et al., 1984; Eichelberger et al., 1985) who reported that buffer supplementation (0.25 to 1.2% $NaHCO_3$) in alfalfa hay had no significant effect on nutrient digestion. Similarly, its supplementation in hay crop silage did not significantly affect nutrient digestion (Stokes and Bull, 1986). However, Rogers et al. (1985) reported that supplementation of $NaHCO_3$ (1.4%) improved DM, organic matter (OM) and crude protein (CP) digestibilities in dairy cows fed alfalfa hay based diet. Stokes and Bull, (1986) also observed that supplementation of $NaHCO_3$ in corn silage based diets enhanced the DM, OM, ADF, gross energy and cellulose digestibilities in early lactating cows. Other workers (Erdman et al., 1982; Snyder et al., 1983) also pointed out improved DM, OM, ADF and NDF digestibilities in dairy animals when $NaHCO_3$ was supplemented in their diets. Rogers et al. (1982) observed that DM digestibility increased in cows when fed 2.0% $NaHCO_3$ in a mixed ration of 75% concentrate and 25% corn silage diet. This improved DM and NDF digestibilities might be due to reduced flow rate at the duodenum level (Tagari et al., 1982).

Alkaline nature of high DCAD diet or sodium bicarbonate feeding may be used as a nutritional tool to enhance rumen ecology aimed to utilize nutrients more efficiently, however, its response in terms of nutrients utilization depends on the nature of diet, rumen dynamics (which may differ with age) and productive potential, etc.

BLOOD ACID BASE STATUS

A positive linear relationship exists between blood acid base status and DCAD level (Jackson et al., 1992). It was observed that blood pH and HCO_3^- were lower in calves fed 0 DCAD diet than those fed 21, 37 and 52 mEq/100 g of DM DCAD diets (Jackson et al., 1992). Similarly, Roche et al. (2005) also reported that altering DCAD from 23 to 88 mEq/100 g of DM increased blood pH and HCO_3^- concentration in early lactating cows. The main reason for reduced blood pH and HCO_3^- at low DCAD diet is due to its acidic properties. Calcium chloride is primarily used as an anionic salt to reduce the DCAD level which has more absorption and acidifying properties compared to all other anionic salts. Chloride is absorbed from the posterior part of the intestine in exchange of Na^+ and when it is in excess of Na^+ then with HCO_3^- resulting in reduced blood bicarbonate and increased H^+. It might have overcome the capacity of kidneys to excrete H^+ to maintain a constant blood pH, following slight metabolic acidosis. Moreover, when the body faces an acid load, it is compensated through respiratory rate that reduced partial pressure of carbon (iv) oxide (pCO_2) and carbonic acid (H_2CO_3) (Hill, 1990). Other researchers (Borucki Castro et al., 2004; Chan et al., 2006; Apper-Bossard et al., 2006; Shahzad et al., 2007; Li et al., 2008; Sarwar et al., 2008) also reported similar findings.

Moore et al. (2000) reported that blood pH and HCO_3^- were lower in cows and heifers fed –15 DCAD diet than those fed 0 DCAD diet. Cows fed low DCAD diets (-40, -51 and -63 mEq/kg of DM) had reduced blood pH than those fed high DCAD diet (+203 mEq/kg of DM), although the difference was not significant (Vagnoni and Oetzel, 1998). Similarly, Roche et al. (2003a) also reported significant reduction in blood pH in cows fed +21 DCAD diet compared to those fed +45, +70 and +95 mEq/100 g DCAD diets. These studies were in line with Fredeen et al. (1988b) who reported that blood pH and HCO_3^- increased with increasing DCAD from 0.7 to 90 mEq/100 g DM in pregnant and lactating goats. High DCAD diets decreased blood H^+ and thus resulted in increased blood HCO^-_3 (Block, 1994) as blood HCO_3^- responses were inversely related to H^+ changes that reflected the metabolic nature of the acid challenge at low DCAD diet. Outcome of the studies suggest significant influence of high DCAD diet on acid base status of the animals through modification in blood pH due to alteration in blood bicarbonate and H^+ concentrations.

BLOOD MINERALS

It has been observed that plasma Ca concentration was higher in prepartum cows fed low DCAD diet compared to those fed high DCAD diet (Tucker et al., 1992). Feeding anionic diets before and after parturition improved total Ca in cows (Oetzel et al., 1988). Other workers (Yen et al., 1981; Tucker et al., 1991; Li et al., 2008; Wu et al., 2008) also reported similar findings. Improved plasma Ca concentration is due to increased Ca absorption (Verdaris and Evans, 1975), Ca mobilization from bones (Fredeen et al., 1988a) and renal reabsorption of Ca due to slight metabolic acidosis induced by low DCAD diet (Ross, 1994b; Shahzad et al., 2008a, b; Sharif et al., 2010). Feeding a low DCAD diet increased the flow of Ca through the readily exchangeable Ca pool (Takagi and Block, 1988) which increased ionized Ca concentration in the blood (Oetzel et al., 1988). The improved Ca status of the animal helps in reducing the occurrence of milk fever at the time of calving.

Serum Na^+ remained unaffected with varying levels of DCAD (West et al., 1991). Tucker et al. (1988) also observed non-significant effect on serum Na^+ or K^+ concentration but Cl^- concentration decreased with increasing DCAD. Similar findings were observed by West et al. (1992) who reported that serum Na^+ and K^+ were not altered when DCAD level was increased from 120.4 to 464.1 mEq/kg DM. A meta-analysis conducted by Hu and Murphy (2004) also revealed similar findings. The non-significant effect of high DCAD diet on Na^+ and K^+ might be due to their excessive excretion through kidney. However, Fredeen et al. (1988b) noticed that plasma Na^+ concentration increased as DCAD was increased in the diet. Low DCAD diets resulted in increased Cl^- concentration in pregnant and lactating goats (Fredeen et al., 1988a) which reflects Cl^- content of the diet (Tucker et al., 1991). Its absorption takes place in ileum and colon part of large intestine in exchange of $HC0_3^-$ (Ganong, 1983). A linear increase in serum cation anion difference was observed with increasing DCAD level in diet (West et al., 1991) which is due to its positive association with blood pH thus improving blood buffering capacity.

The DCAD had non-significant effect on serum Mg concentration (West et al., 1992). However, Roche et al. (2003a) observed a linear increase in renal excretion of Mg concentration as DCAD level was decreased in the diet. Other researchers (Fredeen et al., 1988b; Roche et al., 2005; Sarwar et al., 2007a, b) also observed similar findings. It might be due to metabolic acidosis induced by low or negative DCAD diet. The DCAD had non-significant effect on serum P concentration (West et al., 1992; Tucker et al., 1988). Contrary to this, Roche et al. (2005) reported increased plasma P concentration as DCAD was increased in the diet. Delaquis and Block (1995b) observed increased plasma sulfide (S^{2-}) concentration with decreasing DCAD in the diet which might be due to renal regulation for its absorption. Studies on DCAD suggest that feeding low DCAD diets may increase serum Ca concentration which can be helpful in reducing the occurrence of milk fever at the time of calving.

MINERAL BALANCE

Joyce et al. (1997) reported that urinary excretion of Ca was higher in cows fed -7 mEq/100 g DM DCAD diet compared to those fed +30 and +35 mEq/100 g DM DCAD diets. Other researchers (Borucki Castro et al., 2004; Li et al., 2008) also observed increased urinary excretion of Ca at low DCAD diet while it tended to decrease at high DCAD diet. The increase in urinary Ca at low DCAD was due to high plasma Ca concentration. This excess amount of plasma Ca is filtered through kidneys resulting in increased urinary excretion of Ca (Takagi and Block, 1988) as its concentration increased with increasing plasma Ca concentration, blood H^+ and urine H^+. Moreover, higher plasma Ca concentration indicates greater availability of Ca for metabolic functions and is helpful to assess Ca status of the animal. Tucker et al. (1988) observed that urinary mineral composition was closely associated with dietary mineral composition. Urinary Na^+ and K^+ concentrations increased while Cl^-

concentration decreased as DCAD increased from -10 to +20 mEq/100 g DM. Increased urinary Cl^- concentration in cows fed low DCAD (Tucker et al., 1992) might be attributed to increased Cl^- content of the diet (Tucker et al., 1988; 1992). West et al. (1992) also pointed out that urinary Na^+ and K^+ concentration increased in cows fed high DCAD diet while its reverse was true for Cl^- concentration.

The Cl^- content of the anionic diet induced acid load (Budde and crenshaw, 2003) and it is also retained in excess quantity in the body. An increased Cl^- retention with increasing Cl^- intake was also observed by Golz and Crenshaw (1991) in young ones. Due to physiological regulation of osmotic pressure, the excess dietary Cl^- must either be excreted with a counter balance of cations or stored in a body compartment (bone) with a replacement of another anion. Urinary cation anion difference also tended to increase as DCAD level was increased from 120.4 to 464.1 mEq/kg DM (West et al., 1992). Similarly, West et al. (1991) observed a linear increase in urinary cation anion difference with increasing DCAD.

Tucker et al. (1988) also pointed out that increasing DCAD from -10 to +20 mEq/100 g DM increased urinary cation anion difference. This increased urinary cation anion difference at high DACD diet might be attributed to decreased Cl^- content of the diet. Excretion of P tended to increase as DCAD level was decreased in the diet (Shahzad et al., 2008b). This is because urinary excretion of P is positively associated with increased H^+ both in blood and urine (Tucker et al., 1992). They further pointed out that urinary excretion of Mg increased during first week postpartum in cows fed low DCAD diet. Other researchers (Oetzel et al., 1988; Gaynor et al., 1989) also reported similar results. The increase in urinary excretion of Mg is due to its positive association with plasma Mg concentration. When low DCAD diet is fed to the animals, it induces slight metabolic acidosis which results in increased plasma Mg concentration (Roche et al., 2003a), excreting more urinary Mg. It has been concluded that mineral composition of diet may have close association with urinary mineral composition. Feeding low DCAD diet can increase urinary Ca excretion due to slight metabolic acidosis. This increased amount of plasma Ca may be available for various metabolic processes.

NITROGEN BALANCE

The DCAD had non-significant effect on nitrogen intake and excretion in early lactating cows (Delaquis and Block, 1995b). Fecal nitrogen (N) concentration and total N excretion were similar at both DCAD levels (258.1, 55.5mEq/k DM) that resulted in equal absorption of N. although, there was significant increase in protein secretion in milk at high DCAD level but overall N balance was not affected during early lactation. During mid lactation, intake, absorption, retention and balance of N increased in animals fed high DCAD diets that might be associated with increased feed intake (Delaquis and Block, 1995b). No effect of DCAD on N balance was observed during late lactation, which revealed that acid base perturbation was not sufficient to affect the protein metabolism. Similar results were also reported by other researchers (Phrompheteharat et al., 1981; Welbourne et al., 1988). It was observed that DCAD had no significant effect on N intake, digestibility and retention in dry cows (Delaquis and Block, 1995a), which might be due to small difference in DCAD level used in their study. Similarly, Delaquis and Block (1995c) ascribed that urine N was not affected from DCAD levels in cows fed alfalfa hay and corn silage based diets, although slight increase was observed in cows fed alfalfa hay based diets. The probable reason for this might be attributed to higher N content of alfalfa hay than corn silage.

In conclusion, nitrogen metabolism of animals receiving different DCAD concentrations may be influenced due to effect of DCAD on nitrogen utilization; however, it is governed by multiple factors like dietary nitrogen concentration and its utilization in rumen which may be modified by DCAD.

ENERGY BALANCE

Moore et al. (2000) investigated the effect of various DCAD levels (+15, 0 and -15mEq/100 g DM) in prepartum cows. They reported that energy balance was higher (3.75 MCal/d) in heifers fed +15 mEq/100 g DM DCAD diet than those (0.09 MCal/d) fed -15 mEq/100 g DM DCAD diet. Similarly, cows fed high DCAD level (+15 mEq/100 g DM) showed better (8.42 Mcal/d) energy status when compared (6.01 Mcal/d) with cows fed low DCAD level (–15 mEq/100 g DM). This revealed that energy balance was higher both for heifers and cows fed 0 and +15 mEq/100 kg DM DCAD than those fed -15 mEq/100 DM DCAD diet. The decreased energy balance at low DCAD diet was due to reduced DMI. On the other hand, high DCAD diet increased rumen pH (Tucker et al., 1988) that eventually increased DMI leading to improved energy balance.

It has been observed that sodium bicarbonate supplementation in cows fed control rations (50% corn silage, 50% concentrate) improved energy balance than those cows which were fed control rations only (Vicini et al., 1988). The improved energy balance (21.5 vs 15.5 Mcal ME/d) in sodium bicarbonate supplemented cows was due to increased DMI. In short, feeding high DCAD diet may increase energy balance due to increase in dry matter intake and its utilization in ruminant animals.

URINE pH

Urinary pH is generally used as an indicator of metabolic acid or alkali load (Sanchez, 2003; Wu et al., 2008). Any change in urine pH is due to alteration in blood pH which reflects the ability of kidney to withstand change in metabolic challenge. However, there is a minimum (4.5) threshold limit for reduction in urine pH in the mammalian body (McGilvery, 1970; Houpt, 1993). Low DCAD diets resulted in decreased urine pH in goats (Stratton-Phelps and House, 2004). Manna et al. (1999) also observed a linear increase in urine pH as DCAD was increased from 98 to 270 mEq/kg DM. Hu et al. (2007) also reported increased urine pH with increasing DCAD level in the diet. These results were supported by other researchers (West et al., 1992; Pehrson et al., 1999). Decrease in urine pH in low or negative DCAD diets is associated with excess Cl and S inclusion in the diet. Golz and Crenshaw (1991) noticed similar findings when Cl was increased in the diet. Increased urine H^+ at low DCAD diet was due to acidogenic properties of $CaCl_2$ (Tucker et al., 1991). Theses findings were also supported by other researchers (Merck, 1983; Tucker et al., 1988). The findings reflect that increase or decrease in urine pH in DCAD fed animals was because of the alkaline or acidic nature of the diet, respectively, which is the function of salts used for the respective mineral composition.

RESPIRATORY RATE

West et al. (1992) studied the effect of altering DCAD on respiration rate in cows. They observed that increasing DCAD level (120.4 to 456.0mEq/kg DM) increased respiration rate (94 to 102 breaths/min). This is because pCO_2 increased linearly with increasing DCAD that enhanced respiration rate. West et al. (1991) also observed increased respiratory rate with increasing DCAD level in the diet (from -79 to 324 mEq/kg DM). Whereas, low DCAD diet reduced blood pCO_2, which consequently decreased the respiration rate (Jackson et al., 1992; Ross et al., 1994a). Respiratory rate was also higher in cows fed diet rich in cations (Na^+ and K^+) (Schneider et al., 1988). This is due to high concentration of these minerals which neutralize the acidogenic effect of the diet resulting in increased respiration rate. Contrary to these, Fredeen et al. (1988b) reported that low DCAD diets reduced blood HCO_3^- concentration while H^+ concentration increased which resulted in increased respiratory rate. Table 1 shows the effect of dietary cation-anion difference on dry matter intake, blood pH, plasma calcium and urinary Ca excretion, reported in various studies.

MILK FEVER

Oetzel et al. (1988) noticed the effect of altering DCAD (187, –75 mEq/kg DM) on the prevention of milk fever in prepartum cows and reported that cows fed high DCAD diet (187 mEq/kg DM) had more incidences of milk fever compared to those fed low DCAD diet (–75 mEq/kg DM).

Diets containing -100 to -150 mEq/kg of DM DCAD helped in the prevention of milk fever (Sanchez and Blauwickel, 1994). Goff et al. (1991) also reported similar findings. Prepartum diet supplemented with anionic salts improved Ca metabolism which is responsible for the prevention of hypocalcemia at calving (Dishington, 1975; Block, 1984). Cows fed anionic diet had no milk fever while those fed cationic diet had 47.4% incidence of milk fever (Block, 1984). Feeding low DCAD diet in late gestation reduces milk fever by enhancing mobilization of Ca from bones, thus increasing availability of Ca after calving compared with high DCAD diets (Dishington, 1975; Gaynor et al., 1989). This is necessary as serum plasma Ca concen-tration is reduced at the time of parturition due to entrance from the extracellular fluid to mammary glands for the synthesis of colostrum. This excessive loss of Ca from the extracellular fluid must be replenished by absorbing Ca either from the intestines or from the mobilization of bones. Most of the cows are able to meet the Ca requirements from the onset of lactation but in some animals, this homeostatic mechanism fails and these animals show signs of hypocalcemia. If the calcium need is not met from the external source, the animal may develop milk fever. The homeostatic mechanism depends upon animal age, breed, dietary Ca before parturition and DCAD (Goff et al., 1991). High Ca concentration in animal feed such as alfalfa hay may also cause parturient paresis. Actually, Ca being cationic in nature increases the alkalinity of diet and thus reduces the parathyroid hormone (PTH) activity on bone and kidney cell which are required to maintain normal calcium level. While, low DCAD diet increases Ca mobilization from bones by releasing Ca from amorphous Ca-phosphates and Ca-carbonates on bone surfaces (Bushinsky et al., 1985), preventing milk fever.

However, the exact physiological mechanism for prevention of parturient paresis at low DCAD is not clear. There are various views about it. One is that feeding low DCAD diet might have increased Ca absorption due to acidity induced by the diet (Vagg and Payne, 1970; Fredeen et al., 1988a). While, Block (1984) pointed out that increased bone mobilization of Ca rather than increased Ca absorption from the intestinal tract is the primary means by which anionic salts improve Ca metabolism at parturition. This is because PTH and its receptors are located on the surface of bone and renal tissue cells that result in “lock and key” system and PTH stimulates the target cells. At high DCAD level, blood pH becomes alkaline that results in conformational changes in PTH receptors and as a result of which PTH does not recognize its receptors and thus is unable to work on the tissues efficiently. As a result, blood Ca level decreases and hypocalcemia occurs. Cows suffering from milk fever have increased plasma cortisol level (Littledike et al., 1970; Horst and Jorgensen, 1982) that causes immunosuppression at calving. Hypocalcaemia is also associated with loss of uterine muscle tone that leads to uterine

Table 1. The effect of dietary cation-anion difference on dry matter intake, blood pH, plasma calcium and urinary Ca excretion, reported in various studies.

S/N	DCAD (mEq/100 g of DM)	Dry matter intake (kg/d)		Blood pH		Urine pH		Plasma Ca (mg/dL)		Urinary Ca excretion (g/d)		Reference
		At low DCAD	At high DCAD	At low DCAD	At high DCAD	At low DCAD	At high DCAD	At low DCAD	At high DCAD	At low DCAD	At high DCAD	
1	-10, +20	16.8	18.6	7.37	7.43	6.1	7.6	---	---	---	---	Tucker et al., 1988
2	-11.66, +31.24	10.7	15.9	7.32	7.42	5.38	8.30	9.63	9.23	---	---	West et al., 1991
3	+12.04, +45.6	16.4	18.1	7.45	7.49	6.33	8.19	10.54	10.35	---	---	West et al., 1992
4	0, +52	3.79	3.93	7.34	7.38	6.1	8.1	10.10	10.72	5.5	0.17	Jackson et al., 1992
5	0, +45	7.31	7.56	7.38	7.42	---	---	5.33	5.38	---	---	Ross et al., 1994a
6	+32.72, +48.18	10.1	10.2	7.39	7.40	8.51	8.68	---	---	---	---	Delaquis and Block, 1995a
7	-7, +35	---	---	7.42	7.45	7.59	8.35	4.31	3.87	4.23	0.38	Joyce et al., 1997
8	-6.3, +20.3	14.9	16.0	7.39	7.42	7.20	8.33	9.86	9.20	6.87	0.92	Vagnoni and Oetzel, 1998
9	0, +200	3.56	3.61	7.38	7.39	6.80	8.09	11.5	11.5	---	---	Jackson et al., 2001
10	+12.4, +33.3	6.72	10.01	---	---	---	---	---	---	---	---	Mueller et al., 2001
11	-12, +69	---	---	7.40	7.40	7.76	7.90	---	---	---	---	Roche et al., 2003b
12	+14, +45	20.1	20.1	7.42	7.45	7.73	8.36	---	---	2.8	0.64	Borucki Castro et al., 2004
13	-5.57, -6.02	11.8	10.6	---	---	7.15	7.21	9.25	9.02	18.36	15.93	Chan et al., 2006
14	-22, +22	12.09	13.95	7.34	7.43	5.95	7.81	10.98	9.43	1.16	0.78	Sharif, 2007
15	+26.8, +56.1	22.5	22.0	7.42	7.44	---	---	10.5	10.5	---	---	Wildman et al., 2007
16	+5.6, +14	---	---	---	---	6.21	7.28	7.98	7.70	---	---	Roux et al., 2008
17	-26.5, +22.4	13	11.5	7.35	7.95	6.21	8.60	2.18	2.38	17.1	10.4	Li et al., 2008
18	-15, +15	11.87	12.06	7.37	7.41	5.75	7.67	9.02	8.55	---	---	Wu et al., 2008
19	-11, +33	10.2	13.2	7.30	7.50	6.0	8.0	9.90	8.92	1.25	0.788	Shahzad et al., 2008b

prolapse (Risco et al., 1984). Cows recovered from milk fever have 8 times more chances of ketosis and mastitis compared to non-milk fever affected cows. Dystocia, retained placenta, displacement of abomasum and uterine prolapse also increased due to the occurrence of milk fever (Curtis et al., 1983). Thus, low DCAD diet in prepartum animals may be used as an effective practical nutritional tool in reducing the incidence of milk fever and other problems associated with productivity. Table 2 shows the effect of dietary cation-anion difference on occurrence of milk fever observed in various studies.

MILK YIELD AND COMPOSITION

The effects of dietary cation-anion difference on milk yield as reported in various studies are shown in Table 3. Tucker et al. (1988) observed increased milk yield (18.5 to 20.1 kg) in lactating cows as DCAD level was increased from -10 to +20 mEq/100 g DM. Increasing DCAD improved milk yield, milk fat and milk lactose contents (Mooney and Allen, 2002). Other researchers (West et al., 1991; Delaquis and block, 1995b; Apper-Bossard et al., 2006) also reported similar findings. Hu and Murphy (2004) conducted a meat-analysis and observed optimum milk production at 34 and 40 mEq/100 g DM DCAD. This work was also supported by other data analyzed by Sanchez and Beede (1994) who stated that optimum milk yield can be obtained from lactating animals if the DCAD level is kept in the range of 25 and 50 mEq/100 g DM. Improved milk production at higher DCAD level is due to the reason that a positive correlation exists between DCAD and milk yield (Sanchez et al., 2002) which might be due to improved DMI. It has been observed that higher metabolic activities make cellular environment acidic due to more production

Table 2. The effect of dietary cation-anion difference on occurrence of milk fever, observed in various studies.

S/N	DCAD (mEq/100 g of DM)	Milk fever % incidence or number of cases		Reference
		At low DCAD	At high DCAD	
1	-11.9, +34.6	16.7%	85.7%	Dishington, 1975
2	-17.2, +44.9	0%	47.4%	Block, 1984
3	-7.5, +18.9	4%	17%	Oetzel et al., 1988
4	-3.0, +9.0	4 / 60	5 / 60	Tucker et al., 1992
5	-7, +35	2/15	3/15	Joyce et al., 1997
6	-22, +22	0	40%	Sharif, 2007
7	-11, 33	0	33%	Shahzad et al., 2008b
8	-15, +15	0/10	0/10	Wu et al., 2008

Table 3. The effect of dietary cation-anion difference on milk yield, reported in various studies.

S/N	DCAD (mEq/100g of DM)	Milk yield (kg/d)		Reference
		At low DCAD	At high DCAD	
1	-10, +20	18.5	20.1	Tucker et al., 1988
2	-11.66, +31.24	16.4	19.7	West et al., 1991
3	+12.04, +45.6	22.4	22.0	West et al., 1992
4	-7, +35	29.1	28.9	Joyce et al., 1997
5	+21, +127	25.4	23.2	Roche et al., 2003a
6	+14, +45	29.2	30.3	Borucki Castro et al., 2004
7	+20, +50	25.5	22.4	Chan et al., 2005
8	+0.4, +30.6	29.2	29.3	Apper-Bossard et al., 2006
9	+36.5, +58.5	27.5	27.4	Wildman et al., 2007
10	-15, +15	35.60	33.23	Wu et al., 2008
11	-11, +33	12.60	15.30	Shahzad et al., 2008a

of CO_2 in lactating dairy cows. Feeding high DCAD diet neutralizes the acidity due to its alkalogenic property, which improves cellular glucose intake (Block, 1994) thus improving productive performance of the animal.

Fredeen et al. (1988b) observed the effect of diets containing –2.8, -38.3 and 33.1 mEq/100 g DM DCAD in goats. They reported that milk yield was slightly higher at low DCAD. Similar findings were also reported by Block (1984) who observed 6.8% depression in milk yield in cows fed high DCAD diet (33.05 mEq/100 g DM) than those fed low DCAD diet (-12.85 mEq/100 g DM). This might be attributed to milk fever problem at high DCAD diet during parturition that was responsible for decreased productive span (Block, 1984). Feeding low DCAD diet to close up cows has favorable effect on animal health and production. These diets are helpful in preventing milk fever and associated problems. It has been observed that cows that suffered from milk fever have reduced milk production in subsequent lactations than cows which never suffered from the problem (Moore et al., 2000). Joyce et al. (1997) also reported increased milk production during first few weeks of lactation in cows fed negative DCAD diet (–7 mEq/100 g DM) compared to those fed high DCAD diet (+35 mEq/100 g DM). The probable explanation for this might be the improved Ca status of cows fed low DCAD diet.

Milk protein remained unaffected by DCAD level (Tucker et al., 1988). Aramble et al. (1988) also pointed out that milk protein percent remained unaltered with supplementation of $NaHCO_3$. Roche et al. (2005) observed improved milk fat with increasing DCAD levels in the diet. West et al. (1992) also reported similar findings. This might be due to the reason that high DCAD diet, being alkaline in nature, might have shifted the rumen fermentation pattern to acetate and butyrate production (Kaufmann et al., 1980; Klover and de Veth, 2002) that enhanced *de novo* fatty acids synthesis which led to improved milk fat synthesis. It has been concluded that feeding high DCAD diet may improve milk yield due to increased dry matter intake. It can also be helpful in improving milk fat synthesis due to shifting of rumen fermentation towards acetate and butyrate production in animals fed on high DCAD.

OVARIAN ACTIVITY AND HORMONAL PROFILE

It is well documented that a positive linear relationship exists between energy balance and ovarian activity and a high energy balance stimulates the ovarian functions (Pate, 1999). Feeding high DCAD diets perk up energy balance due to increased DMI which in turn improve ovarian activity (Sharif, 2007). At high DCAD diets, trace minerals enhance reproductive performance in cows by decreasing days to first service, days to conception and services per conception (Uchida et al., 2001). High DCAD diet tended to increase insuline like growth factor (IGF-I) in animals through increased DMI (Moore et al., 2000). The IGF-I is considered an indicator of energy status in dairy animals (Pate, 1999). It has stimulatory effect on granulosa cells to produce more estradiol which in turn improves the ovarian activity (Spicer et al., 1990). High DCAD diets might also have activated steriodogenic enzymes necessary for the synthesis of reproductive hormones such as progesterone and estrogen. These hormones are secreted mainly from follicles and corpus luteum and are responsible for ovulation and pregnancy, respectively.

Low DCAD diet is responsible for reduced ovarian efficiency due to depressed DMI (Sharif et al., 2009). Decreased DMI also increases the occurrence of negative energy balance and postpartum anovulation (Canfield and Butler, 1991; Beam, 1996; Zurek et al., 1995). Negative energy balance causes less secretion of leutinizing hormone (Schillo, 1992) which results in reduced follicular growth and ovulation. During negative energy balance, estrus is delayed due to less hormonal concentrations and their activity. It also reduces functions of corpus luteum. However, feeding low DCAD diet pre-partum has favorable effect on reproductive performance. Beede et al. (1991) observed that prepartum cows offered low DCAD diets had 71% conception rate while those fed high DCAD diets had 54% in the coming oestrous. They further observed 124 and 138 days open for low and high DCAD diets, respectively. Wang et al. (1991) also found that prepartum cows fed low DCAD diets had higher pregnancy rate compared to those fed high DCAD diets. It might be due to sufficient Ca availability, which not only met body needs but also quickened the involution process that resultantly increased the conception rate and reduced the days open. In short, feeding high DCAD diet improved energy balance due to increased DMI which may stimulate the ovarian functions thus, improving the reproductive performance of the animal.

MASTITIS AND UDDER EDEMA

Low DCAD diets reduced the incidence of mastitis; metritis and displacement of abomasum compared to those cows fed high DCAD diets (Goff and Horst, 1997, 1998). These diets increased serum Ca status of the animal. Melendez et al. (2002) reported that cows offered anionic salts had higher plasma Ca concentration compared to those offered high DCAD diets. Adequate Ca level is very essential for normal physiological and muscular functions of the animal. Low DCAD diet prepartum has positive effect on Ca metabolism, prepartum health and post-partum productive and reproductive performance (Horst et al., 1997). If the animal is hypocalcemic at parturition, it will impair smooth muscles contraction that is very imperative for the closing of teat sphincter after milking. Smith et al. (1985) reported that animals are more prone to mastitis during first week of the dry period or first month of lactation which may be due to failure of the bacteria to flush from the teat canal. Metabolic disorders like milk fever and ketosis are also closely associated with retained placenta, mastitis and metritis (Dohoo and Martin, 1984; Correa et al., 1993).

Lema et al. (1992) reported that prepartum cows fed high DCAD diets developed sever udder edema compared to those fed $CaCl_2$ diet. Removal of $CaCl_2$ from the diet increased the chances of udder edema. Heifers fed high amounts of NaCl and $KHCO_3$ tended to develop edema promptly compared to those fed low amounts of these salts (Nestor et al., 1988). Excess intake of Na or K (high DCAD diets) may be the major cause of udder edema (Al-Ani and Vestweber, 1986; Vestweber and Al Ani, 1983). Other researchers (Randall et al., 1974; Conway et al., 1977; Sanders and Sanders, 1981; Jones et al., 1984) also reported that high DCAD diet is the major cause of udder edema and its restriction to pregnant heifers reduce the severity of the problem. Occurrence of udder edema at high DCAD diet might be due to immune suppression in affected animals, manifested by increased plasma cortisol concentration (Littledike et al., 1970). The effect of dietary cation-anion difference on udder edema and mastitis as observed in various studies is shown in Table 4. It has been concluded that mastitis and udder edema can be controlled through manipulation of DCAD levels in the diet.

CONCLUSION AND PERSPECTIVE

Studies on DCAD have confirmed its significant influence in systemic acid base status which has direct and indirect association with not only productive and reproductive performance on ruminants but also, with their well being. However, concentration of DCAD in ruminants differs as per animal productive potential, physiological stage, environmental conditions, diet composition and breed, etc. Furthermore, consequences of feeding DCAD in ruminants for longer period of time on productivity and well being are still areas which need to be investigated in order to harvest real benefits associated with animal agriculture enterprise.

Table 4. The effect of dietary cation-anion difference on udder edema and mastitis, observed in various studies.

Item	DCAD (mEq/100g of DM)	Incidence or number of cases		Reference
		At low DCAD	At high DCAD	
[1]Udder edema	-22, +22	0	6.5	Sharif, 2007
Udder edema	-15, +15	1/10	2/10	Wu et al., 2008
[2]Mastitis	-22, +22	0	2.5	Sharif, 2007
Mastitis	-15, +15	1/10	1/10	Wu et al., 2008

[1]0 = No problem, 10 = severe problem.
[2]0 = no problem, 3 = severe problem.

REFERENCES

Al-Ani FK, Vestweber JGE (1986). Udder edema. An updated review. Vet. Bull. 56: 763-769.

Apper-Bossard E, Peyraud JL, Faverdin P, Meschy F (2006). Changing dietary cation anion difference for dairy cows fed with two contrasting levels of concentrate in diets. J. Dairy Sci. 89: 749-760.

Aramble MJ, Wiedmeier RD, Clark DH, Lamb RC, Boman RL, Walterk JL (1988). Effect of sodium bicarbonate and magnesium oxide in alfalfa based total mixed ration fed to early lactating dairy cattle. J. Dairy Sci. 71: 159-163.

Bauman DE, Griinari JM (2003). Nutritional regulation of milk fat synthesis. Annu. Rev. Nutr. 23: 203-227.

Beam SW (1996). Energy balance, follicular growth and first ovulation in postpartum dairy cows. J. Dairy Sci. 79: 127-132.

Beede DK, Risco CA, Donovan GA, Wang C, Archbald LF, Sanchez WK (1991). Nutritional management of the late pregnant dry cow with particular reference to dietary cation-anion difference and calcium supplementation. In Proc. 24th Amer. Assoc. Bovine Pract, Stillwater, OK.

Block E (1984) Manipulating dietary anions and cations for prepartum dairy cows to reduce incidence of milk fever. J. Dairy Sci. 67: 2939-2948.

Block E (1994) Manipulation of dietary cation-anion difference on nutritionally related production diseases, productivity, and metabolic responses of dairy cows. J. Dairy Sci. 77: 1437-1450.

Borucki CSI, Phillip LE, Girard V, Tremblay A (2004). Altering dietary cation-anion difference in lactating dairy cows to reduce phosphorus excretion to the environment. J. Dairy Sci. 87: 1751-1757.

Budde RA, Crenshaw TD (2003). Chronic metabolic acid load induced by changes in dietary electrolyte balance increased chloride retention but did not compromise bone in growing swine. J. Anim. Sci. 81: 197-208.

Bushinsky DA, Riera GS, Favus MJ, Coe FL (1985). Response of serum 1,25(OH)2D3 to variation of ionized calcium during chronic acidosis. Am. J. Physiol. 249: 361-365.

Butler WR, Everett RW, Coppock CE (1981). The relationships between energy balance, milk production and ovulation in postpartum Holstein cows. J. Anim. Sci. 53: 742-748.

Canale CJ, Stokes MR (1988). Sodium bicarbonate for early lactation cows fed corn silage or hay crop silage-based diets. J. Dairy Sci. 71: 373-380.

Canfield RW, Butler WR (1991). Energy balance, first ovulation and the effects of nalaxone on LH secretion in early postpartum dairy cows. J. Anim. Sci. 69: 740-746.

Chan PS, West JW, Bernard JK (2006). Effect of prepartum dietary calcium on intake and serum and urinary mineral concentrations of cows. J. Dairy Sci. 89: 704-713

Chan PS, West JW, Bernard JK, Fernandez JM (2005). Effects of dietary cation-anion difference on intake, milk yield, and blood components of the early lactation cow. J. Dairy Sci. 88: 4384-4392.

Conway JF, Olson HH, McGoy GC (1977). Effects of sodium chloride supplementation on the incidence of and severity of mammary edema and on the serum sodium levels in per-parturient cows and heifers. J. Dairy Sci. p. 110.

Correa MT, Erb H, Scarlett J (1993). Path analysis for seven postpartum disorders of Holstein cows. J. Dairy Sci. 76: 1305-1312.

Curtis CR, Erb HN, Sniffen CJ, Smith RD, Powers PA, Smith MC, White ME, Hillman RB, Pearson EJ (1983). Association of parturient hypocalcemia with eight periparturient disorders in Holstein cows. J. Am. Vet. Med. Assoc. 183: 559-561.

Delaquis AM, Block E (1995a). Acid-base status, renal function, and macromineral metabolism of dry cows fed diets differing in cation-anion difference. J. Dairy Sci. 78: 604-619.

Delaquis AM, Block E (1995b). The effects of changing ration ingredients on acid-base status, renal function, and macromineral metabolism. J. Dairy Sci. 78: 2024-2039.

Delaquis AM, Block E (1995c). Dietary cation-anion difference, acid-base status, mineral metabolism, renal function, and milk production in lactating dairy cows. J. Dairy Sci. 78: 2259-2284.

DePeters EJ, Fredeen AH, Bath DL, Smith NE (1984). Effect of sodium bicarbonate addition to alfalfa hay-based diets on digestibility of dietary fractions and rumen characteristics. J. Dairy Sci. 67: 2344-2355.

Dishington IW (1975). Prevention of milk fever (hypocalcemic paresis puerperalis) by dietary salt supplementation. Acta Vet. Scand. 16: 503-512.

Dohoo IR, Martin SW (1984). Disease, production and culling in Holstein Friesian cows. IV. Effects of disease on production. Prev. Vet. Med. 2: 755-770.

Doreau M, Chilliard Y, Rulquin H, Demeyer P (1999). Manipulation of milk fat in dairy cows. Recent Advances in Animal Nutrition. P. C. Garnsworthy, J. Wiseman, edn. Nottingham University Press, Nottingham, UK. pp. 81-109.

Eichelberger RC, Mulier LD, Sweeney TF, Abrams SM (1985). Addition of buffers to high quality alfalfa hay-based diets for dairy cows in early lactation. J. Dairy Sci. 68: 1722-1731.

Erdman RA, Hemken RW, Bull LS (1982). Dietary sodium bicarbonate and magnesium oxide for early postpartum lactating dairy cows. effects on production, acid base metabolism and digestion. J. Dairy Sci. 65: 712-731.

Escobosa A, Coppock CE, Rowe LD, Jenlrins WL, Gates CE (1984). Effects of dietary sodium bicarbonate and calcium chloride on physiological responses of lactating dairy cows in hot weather. J. Dairy Sci. 67: 574-584.

Espino L, Guerrero F, Suarez ML, Santamarina G, Goico A, Fidalgo LE (2003). Long term effects of dietary cation anion difference on acid base status and bone morphology in reproducing ewes. J. Vet. Med. 50: 488-495.

Fredeen AH, DePeters EJ, Baldwin RL (1988a). Effects of acid base disturbances caused by differences in dietary fixed ion balance on kinetics of calcium metabolism in ruminants with high calcium demand. J. Anim. Sci. 66: 174-184.

Fredeen AH, DePeters EJ, Baldwin RL (1988b). Characterization of acid-base disturbances and effects on calcium and phosphorus balances of dietary fixed ions in pregnant or lactating does. J. Anim. Sci. 66: 159-165.

Ganong WF (1983). Review of Medical Physiology. 11th edn. Lange Med. Publ Los Altos, CA.

Gaynor PJ, Mueller FJ, Miller JK, Ramsey N, Goff JP, Horst RL (1989).

Parturient hypocalcemia in Jersey cows fed alfalfa haylage based diets with different cation to anion ratios. J. Dairy Sci. 72: 2525-2531.
Goff JP, Horst RL (1997). Physiological changes at parturition and their relationship to metabolic disorders. J. Dairy Sci. 80: 1260-1268.
Goff JP, Horst RL (1998). Factors to concentrate on to prevent periparturient disease in the dairy cow with special emphasis on milk fever. In Proc. 31st Conf. of American Association of Bovine Practioners, Spokane, WA. pp 154-163.
Goff JP, Horst RL, Beitz DC, Littledike ET (1988). Use of 24-F-1,25-dihydroxyvitamin D3 to prevent parturient paresis in dairy cows. J. Dairy Sci. 71: 1211-1219.
Goff JP, Horst RL, Mueller FJ, Miller JK, Kiess GA, Dowlen HH (1991). Addition of chloride to a prepartal diet high in cations increases 1, 25-dihydroxyvitamin D response to hypocalcemia preventing milk fever. J. Dairy Sci. 74: 3863-3871.
Golz DI, Crenshaw TD (1991). The effect of dietary potassium and chloride on cation-anion balance in swine. J. Anim. Sci. 69: 2504–2515.
Gröhn YT, Erb HN, McCulloch CE, Saloniemi HS (1989). Epidemiology of metabolic disorders in dairy cattle. associations among horst characteristics, disease and production. J. Dairy Sci. 72: 1876-1885.
Hill LL (1990). Body composition, normal electrolyte concentrations and maintenance of normal volume, tonicity and acid base metabolism. Pediatr. Clin. North Am. 37: 241-256.
Horst RL, Goff JP, Reinjardt TA, Buxton DR (1997). Strategies for preventing milk fever in dairy cattle. J. Dairy Sci. 80: 1269-1280.
Horst RL, Jorgensen NA (1982). Elevated plasma cortisol during induced and spontaneous hypocalcemia in ruminants. J. Dairy Sci. 65: 2332-2337.
Houpt TR (1993). Acid base balance. Dukes' Physiology of Domestic animals. 11th edn. M. J. Swenson. Ed. Cornell Univ. Press, Ithaca, NY. pp. 604-615.
Hu W, Kung Jr. L, Murphy MR (2007). Relationships between dry matter intake and acid–base status of lactating dairy cows as manipulated by dietary cation–anion difference. Anim. Feed Sci. Technol. 136: 216-225.
Hu W, Murphy MR (2004). Dietary Cation-Anion Difference Effects on Performance and Acid-Base Status of Lactating Dairy Cows. A Meta-Analysis. J. Dairy Sci. 87: 2222-2229.
Jackson JA, Akay V, Franklin ST, Aaron DK (2001). Effect of cation-anion difference on calcium requirement, feed intake, body weight gain, and blood gasses and mineral concentrations of dairy calves. J. Dairy Sci. 84: 147-153.
Jackson JA, Hopkins DM, Xin Z, Hemken RW (1992). Influence of cation anion balance on feed intake, body weight gain, humoral response of dairy calves. J. Dairy Sci. 75: 1281-1286.
Jones TO, Knight R, Evans RK (1984). Chronic udder edema in milking cows and heifers. Vet. Record, 115: 218-219.
Joyce PW, Sanchez WK, Goff JP (1997). Effect of anionic salts in prepartum diets based on alfalfa. J. Dairy Sci. 80: 2866-2875.
Kaufmann W, Hagemeister H, Dirksen G (1980). Adaptations to changes in dietary composition, level and frequency of feeding, in digestive physiology and metabolism in ruminants. Y Ruckebusch and P Thivend, ed Avi publ Co Westport, CT. p. 587.
Klover ES, de Veth MJ (2002). Prediction of ruminal pH from pasture-based diets. J. Dairy Sci. 85: 1255-1266.
Lema M, Tucker WB, Aslam M, Shin IS, Le Ruyet P, Adams GD (1992). Influence of calcium chloride fed prepartum on severity of edema and lactational performance of dairy heifers. J. Dairy Sci. 75: 2388-2393.
Li FC, Liu HF, Wang ZH (2008). Effects of dietary cation-anion difference on calcium, nitrogen metabolism and relative blood traits of dry Holstein cows. Anim. Feed Sci. Technol. 142: 185-191.
Littledike ET, Whipp SC, Witzel DA, Baetz AL (1970). Insulin corticoids and parturient paresis. Academic Press, New York.
Manna AF, Owens FN, Janloo S, Ahmad YH, Welty SD (1999). Impact of dietary cation anion balance on water intake and physiological measurements of feedlot cattle. Animal Science Research Report. Department of Animal Science, Ohio state university, USA. pp. 152-158.
McGilvery RW (1970). Respiratory exchange and H+ balance. Biochemistry, A functional approach. W. B. Saunders, Philadelphia, PA. pp. 608-628.
Melendez P, Donovan A, Risco CA, Hall MB, Littell R, Goff J (2002). Metabolic responses of transition Holstein cows fed anionic salts and supplemented at calving with calcium and energy. J. Dairy Sci. 85: 1085-1092.
Merck I (1983). 10th edn. Merck and Co Inc Rahway, NY.
Mongin P (1981). Recent advances in dietary cation anion balance. Applications in poultry. Proc. Nutr. Soc. 40: 285-294.
Moore SJ, Vandehaar MJ, Sharma K, Pilbeam TE, Beede DK, Bucholtz F, Liesman JS, Horst RL, Goff JP (2000). Effect of altering dietary cation and anion difference on calcium and energy metabolism in prepartum cows. J. Dairy Sci. 83: 2095-2104.
Mueller RK, Cooper SR, Topliff DR, Freeman DW, MacAllister C, Carter SD (2001). Effect of dietary cation-anion difference on acid-base status and energy digestibility in sedentary horses fed varying levels and types of starch. J. Equine Vet. Sci. 21: 498-502.
Nestor KE, Hemken Jr. RW, Harmon RJ (1988). Influence of sodium chloride and potassium bicarbonate on udder edema and selected blood parameters. J. Dairy Sci. 71: 366-372.
Oetzel GR (1993). Use of anionic salts for prevention of milk fever in dairy cattle. Compendium Cont. Ed. Pract. Vet. 15: 1138-1146.
Oetzel GR, Barmore JA (1993). Intake of a concentrate mixture containing various anionic salts fed to pregnant, nonlactating dairy cows. J. Dairy Sci. 76: 1617-1623.
Oetzel GR, Olson JD, Curtis CR, Fettman MJ (1988). Ammonium chloride and ammonium sulfate for prevention of parturient paresis in dairy cows. J. Dairy Sci. 71: 3302-3309.
Olson JD (1991). Relationship of nutrition to abomasal displacement and parturient paresis. Bov. Prac. No 26: 88-91.
Osmanu ST (1979). Studies on bovine infertility at the Agricultural Research Station (Legon) over half a decade (1972-77). Ghana University, Department of Animal Science Studies, Legon, Ghana. p. 82.
Pate JL (1999). Effects of energy balance on ovarian function. Tristate-State Dairy Nutrition Conference. April 20-21. Ohio, USA.
Pehrson B, Svensson C, Gruvaeus I, Rirkki M (1999). The influence of acidic diets on the acid-base balance of dry cows and the effect of fertilization on mineral content of grass. J. Dairy Sci. 82: 1310-1317.
Phromphetcharat V, Jackson A, Dass PD, Welbourne TC (1981). Ammonia portioning between glutamine and urea. interogan participation in metabolic acidosis. Kidney Int. 20: 598-605.
Randall WE, Hemken RW, Bull LS, Douglas LW (1974). Effect of dietary sodium and potassium on udder edema in Holstein heifers. J. Dairy Sci. 57: 472-475.
Risco CA, Reynolds JP, Hird D (1984). Uterine prolapse and hypocalcemia in dairy cows. J. Am. Vet. Med. Assoc. 185: 1517-1519.
Roche JR, Dalley D, Moate P, Grainger C, Rath M, Mara FO (2003a). Dietary cation anion difference and the health and production of pasture fed dairy cows. 1. Dairy cows in early lactation. J. Dairy Sci. 86: 970-978.
Roche JR, Dalley D, Moate P, Grainger C, Rath M, Mara FO (2003b). Dietary cation -anion difference and the health and production of pasture-fed dairy cows 2.non-lactating prepartum cows. J. Dairy Sci. 86: 979-986.
Roche JR, Petch S, Kay JL (2005). Manipulating the dietary cation anion difference via drenching to early lactating dairy cows grazing pasture. J. Dairy Sci. 88: 264-276.
Rogers JA, Davis CL, Clark JH (1982). Alteration of rumen fermentation, milk fat synthesis, and nutrient utilization with mineral salts in dairy cows. J. Dairy Sci. 65: 577-586.
Rogers JA, Muller LD, Snyder TJ, Maddox TL (1985). Milk production, nutrient digestion, and rate of digesta passage in dairy cows fed long or chopped alfalfa hay supplemented with sodium bicarbonate. J. Dairy Sci. 68: 868-880.
Ross JG, Spears JW, Garlich JD (1994a). Dietary electrolyte balance effects on performance and metabolic characteristics in finishing steers. J. Anim. Sci. 72: 1600-1607.
Ross JG, Spears JW, Garlich JD (1994b). Dietary electrolyte balance effects on performance and metabolic characteristics in growing steers. J. Anim. Sci. 72: 1842-1848.
Roux ML, Johnston SL, Lirette RD, Bidner TD, Southern LL, Jardon PW (2008). The effect of diets varying in dietary cation-anion difference

fed in late gestation and in lactation on sow productivity. The Profession Anim. Sci. 24: 149-155.
Sanchez WK (2003). The latest in dietary cation-anion difference (DCAD) nutrition. Proceeding of 43nd Annual Dairy Cattle Day 26th March .Main Theater. University of California. Davis Campus.
Sanchez WK, Beede DK (1994). Cation-anion concepts for lactating dairy rations. Cation-anion applications for lactating dairy cattle. in Proceedings of Mallinckrodt Feed Ingredients Conference. Rochester, NY. pp. 1-13.
Sanchez WK, Blauwickel R (1994). Prevention of milk fever by application of dietary cation-anion balance concept. Cooperative extension. Washington, State University, Subject code 130A, pp. 1-8.
Sanchez WK, DeGroot MA, Block E, Weber D, Cummings KR (2002). Production and economics responses of high production lactating dairy cows to increasing dietary cation anion difference during non-heat stress season. J. Dairy Sci. 1: p. 85.
Sanders DE, Sanders JA (1981). Chronic udder edema in dairy cows. J. Am. Vet. Med. Assoc. 178: 1273-1274.
Sarwar M, Shahzad MA, Nisa M (2007a). Influence of varying level of sodium bicarbonate on milk yield and its composition in early lactating *Nili Ravi* buffaloes. Asian Aust. J. Anim. Sci. 20: 1858-1864.
Sarwar M, Shahzad MA, Nisa M (2007b). Nutrients intake, acid base status and growth performance of growing thalli lambs fed varying level of dietary cation anion difference. Asian Aust. J. Anim. Sci. 20: 1713-1720.
Sarwar M, Shahzad MA, Nisa N (2008). Nutrient intake, acid base status and growth performance of growing *Barbari* goats fed varying level of dietary cation anion difference. The 13th Animal Science Congress of the Asian Australasian Association of Animal Production Societies. Hanoi, Vietnam.
Schillo KK (1992). Effects of dietary energy on control of leutinizing hormone secretion in cattle and sheep. J. Anim. Sci. 70: 1271-1282.
Schneider PL, Beede DK, Wilcox CJ (1988). Nycterohemeral patterns of acid-base status, mineral concentrations and digestive function of lactating cows in natural or heat stress environments. J. Anim. Sci. 66: 112-125.
Shahzad MA, Sarwar M, Nisa N (2007). Nutrient intake, acid base status and growth performance of growing male buffalo calves fed varying level of dietary cation anion difference. Lives Sci. 111: 136-143.
Shahzad MA, Sarwar M, Nisa N (2008a) Influence of altering dietary cation anion difference on milk yield and its composition of early lactating *Nili Ravi* buffaloes in summer. Lives Sci. 113: 133-143.
Shahzad MA, Sarwar M, Nisa N (2008b). Influence of varying dietary cation anion difference on serum minerals, mineral balance and hypocalcemia in *Nili Ravi* buffaloes. Lives Sci. 113: 52-61.
Sharif M (2007). Effect of varying levels of dietary cation anion difference on the performance of Nili Ravi buffaloes in winter. Ph.D. Thesis, University of agriculture, Faisalabad, Pakistan.
Sharif M, Shahzad MA, Nisa M, Sarwar M (2010). Influence of varying levels of dietary cation anion difference on nutrient intake, ruminal characteristics, nitrogen metabolism and in situ digestion kinetics in Nili Ravi buffalo bulls. Anim. Sci. J. doi: 10.1111/j.1740-0929.2010.00780.x
Sharif M, Shahzad MA, Nisa M, Sarwar M (2009). Nutrients intake and ovarian profile as affected by cationic anionic diets in *Nili Ravi* buffaloes in winter. The 6th Asian Buffalo Congress. University of Veterinary and Animal Sciences, Lahore, Pakistan.
Smith KL, Todhunter DA, Schoenberger PS (1985). Environmental mastitis.cause, prevalence, prevention. J. Dairy Sci. 73: 1531-1553.
Snyder TJ, Rogers JA, Muller LD (1983). Effects of 1.2% sodium bicarbonate with two ratios of corn silage grain on milk production, rumen fermentation, and nutrient digestion by lactating cows. J. Dairy Sci. 66: 1290-1297.
Spanghero M (2004). Prediction of urinary and blood pH in nonlactating dairy cows fed anionic diets. Anim. Feed Sci. Technol. 116: 83-92.
Spicer LJ, Thatcher WW, Clark JH (1990). Insulin-like growth factor-I in dairy cows. Relationship among energy balance, body condition, ovarian activity, and estrous behavior. J. Dairy Sci. 73: 929-937.
Stevenson JS, Britt JH (1980). Models for the prediction of days to first ovulation based on changes in endocrine and non-endocrine traits during the first two weeks postpartum in Holstein cows. J. Anim. Sci. 50: 103-112.
Stewart PA (1981). How to understand acid-base-A quantitive acid-base primer for biology and medicine. Edward Arnold, London, UK.
Stokes MR, Bull LS (1986). Effects of sodium bicarbonate with three ratios of hay crop silage to concentrate for dairy cows. J. Dairy Sci. 69: 2671-2680.
Stratton-Phelps M, House JK (2004). Effect of a commercial anion dietary supplement on acid-base balance, urine volume, and urinary ion excretion in male goats fed oat or grass hay diets. Am. J. Vet. Res. 65: 1391-1397.
Tagari H, Reddy NS, Satter LD (1982). Effect of magnesium oxide and sodium bicarbonate on the environment and digestion in the rumen and gastrointestinal tract of lactating cows. J. Anim. Sci. p. 468.
Takagi H, Block E (1988). Effect of manipulatiq dietary anioncation balance on calcium kinetics in normocalcemic and EGTA-infased sheep. J. Dairy Sci. 71Suppl. 1: p. 153 Abstr.
Tucker WB, Adams GD, Lema M, Aslam M, Shin IS, Le Ruyet P, Weeks DL (1992). Evaluation of a system for rating edema in dairy cattle. J. Dairy Sci. 75: 2382-2387.
Tucker WB, Harrison GA, Hemken RW (1988). Influence of dietary cation-anion balance on milk, blood, urine, and rumen fluid in lactating dairy cattle. J. Dairy Sci. 71: 346-352.
Tucker WB, Hogue JF, Adams GD, Aslam M, Shin IS, Morgan G (1992). Influence of dietary cation-anion balance during the dry period on the occurrence of parturient paresis in cows fed excess calcium. J. Anim. Sci. 70: 1238-1250.
Tucker WB, Hogue JF, Waterman DF, Swenson TS, Xin BZ, Hemken RW, Jackson JA, Adams GD, Spicer LJ (1992). Sulfur should be included when calculating the dietary cation-anion balance of diets for lactating dairy cows. Anim Sci Res Rep Oklahoma Res. Stat Oklahoma City, OK, pp. 141-150.
Tucker WB, Xin BZ, Henken RW (1991). Influence of calcium chloride on systemic acid-base status and calcium metabolism in dairy heifers. J. Dairy Sci. 74: 1401-1409.
Uchida K, Mandebvu P, Ballard CS, Sniffen CJ, Carter MP (2001). Effects of feeding Availa-4 on performance of early lactation high producing dairy cows. Anim. Feed Sci. Technol. 93: 193-203.
Vagg MJ, Payne JM (1970). The effect of ammonium chloride-induces acidosis on calcium metabolism in ruminants. Br. Vet. J. 126: 531-537.
Vagnoni BD, Oetzel GR (1998). Effect of dietary cation-anion difference on acid-base status of dry cows. J. Dairy Sci. 81: 1643-1652.
Verdaris JN, Evans LL (1975). Diet calcium and pH versus mineral balance in Holstein cows 84 days pre- to 2 days postpartum. J. Dairy Sci. 59: 1271-1277.
Vestweber JGE, Al-Ani FK (1983). Udder edema in cattle. Compend. Contin. Educ. Pract. Vet. 5: 5-12.
Vicini JL, Cohick WS, Clark JH (1988). Effects of feed intake and sodium bicarbonate on milk production and concentrations of hormones and metabolites in plasma of cows. J. Dairy Sci. 71: 1232-1238.
Wang C, Beede DK, Donovan GA, Archbald LF, DeLorenzo MA, Sanchez WK (1991). Effects of dietary negative cation-anion difference and high calcium content prepartum on calcium metabolism, health, lactational and reproductive performance of Holstein cows. J. Dairy Sci. pp. 275.
Welbourne TC, Givens G, Joshi S (1988). Renal ammoniagenic response to chronic acid loading. role of glucocorticoids. Am. J. Physiol. 254: 134-138.
West JW (1993). Cation-anion balance. Its role in lactating cow nutrition. Feedstuffs, 10: 14-15.
West JW, Haydon KD, Mullinix BG, Sandifer TG (1992). Dietary cation-anion balance and cation source effects on production and acid-base status of heat-stressed cows. J. Dairy Sci. 75: 2776-2786.
West JW, Mullinix BG, Sandifer TG (1991). Changing dietary electrolyte balance for dairy cows in cool and hot environments. J. Dairy Sci. 74: 1662-1671.
Wildman CD, West JW, Bernard JK (2007). Effects of dietary cation-anion difference and potassium to sodium ratio on lactating dairy cows in hot weather. J. Dairy Sci. 90: 970-977.
Wilson G, Stevenson M (1998). Calcium crucial both sides of calving. New Zealand Dairy Exporter, pp. 32.

Wu WX, Liu JX, Xu GZ, Ye JA (2008). Calcium homeostasis, acid-base balance, and health status in periparturient Holstein cows fed diets with low cation-anion difference Lives. Science, 117: 7-14.
Yen JT, Pond WG, Prior RL (1981). Calcium chloride as a regulator of feed intake and weight gain in pigs. J. Anim. Sci. 52: 778-782.
Zurek E, Foxcroft GR, Kennelly JJ (1995). Metabolic status and interval to first ovulation in postpartum dairy cows. J. Dairy Sci. 78: 1909-1920.