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Alterations in hematology, immunology, inflammatory markers, liver, and kidney functions in periparturient Holstein-Friesian cows fed acidogenic diet.

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ABSTRACT

The objective of this study was to evaluate the effect of feeding a negative dietary cation-anion difference during peripartum period on hematological, immunological, and proinflammatory markers in periparturient Holstein-Friesian cattle. Blood samples were collected from 36 periparturient multiparous Holstein-Friesian cows where 18 cows were fed acidogenic diet daily on low dietary cation-anion difference (L-DCAD group, −50 mEq/100 g of DM mEq/100 g of pre-partum matter according to NRC 2012) 21 days before calving, and 18 cows fed normal diet (control). Feeding acidogenic diets during pre-partum period caused leukocytosis and lymphocytosis and significant increase ($P<0.05$) in cortisol and CRP concentration during pre-partum and post-partum periods, and IL-6, IgA, and IgG concentrations during the post-partum period. The liver function tests showed significant ($P<0.05$) increase in GOT, GPT, GGT and ALP in cows feed dietary cation-anion difference (DCAD) compared to control. We concluded that feeding acidogenic diets during pre-partum period on a low DCAD diet might induce immunologic, hepatic, and inflammatory changes that might represent further stress to periparturient dairy cattle the addition of L-DCAD should be under cautions.

1. INTRODUCTION

Many changes occur in metabolic, mineral, acid-base, and immunological status of cows starting from 3 weeks before calving and last for 3 weeks after parturition due to excessive energy and mineral utilization to support the rapid fetal growth and milk production (Pascottini et al., 2020). Dietary cation-anion difference (DCAD) has been defined as the difference in milliequivalents of cations (Na, K) and (Cl, S) per Kilogram of dry matter (DM) and has a direct impact on blood acid-base metabolism. Diets rich in K and Na induce metabolic alkalosis, interfering with tissue sensitivity to parathyroid hormone, and diets rich in Cl and S (anionic salts) cause metabolic acidosis, reducing the risk of hypocalcemia. Consequently, the use of anionic salts has become a popular method to prevent hypocalcemia in dairy cattle (Pedro Melendez et al., 20017). As a result of a mild metabolic acidosis, the activity of PTH will be enhanced, with an expected response of less hypocalcemia around parturition (Goff., 2014). The basic principle of the (DCAD) theory is inspired by strong ion difference (SID) (Megahed et al., 2018). When dairy cows are fed a diet with low DCAD, the number of strong anions absorbed from the intestinal tract will be greater than the number of strong cations, resulting in decreased SID^+. Thereby, a state of strong ion acidosis (metabolic acidosis) is created (Constable et al., 2014). Therefore, feeding a low DCAD diet during the pre-partum period causes slight decrease in blood pH within the normal range. However, urine pH significantly decreases because of the excretion of excessive protons, resulting in aciduria and hypercalciuria (Grünberg et al., 2011).

Diet-induced metabolic acidosis is associated with several deleterious effects in humans and animals, including decreased feed intake, decreased insulin responsiveness and insulin sensitivity, as well as loss of muscle mass, hypertension, and hepatic steatosis (Grünberg et al., 2011; Carnauba et al., 2017). The effects of feeding acidogenic diets on proinflammatory markers and immunological status have not been fully investigated in dairy cattle.

The objective of this study was to characterize the effects of feeding diet-induced metabolic acidosis during peripartum period on hematological, immunological and proinflammatory markers in periparturient Holstein-Friesian dairy cows.

2. MATERIAL AND METHODS

2.1. Study approval:

The study design and protocols were performed under the owner's consent and approved by the Internal Ethics Review Committee of the Faculty of Veterinary Medicine, Benha University, Benha, Egypt. (Protocol Number: BUFVTM 13-12-21).

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2.2. Animals, housing, and feeding:

Blood samples were obtained prospectively from randomly selected 36 multiparous periparturient Holstein-Friesian cows (4-7 years old) from a dairy farm (out of a total 150 dairy cows) in Sharqia governorate between January and May 2020. All cows were kept in free-stall barns. Cows were usually moved from the outdoor to individual box stalls (3.1 × 3.1 m) 21 days before the estimated parturition date. All cows underwent a daily routine health check including California mastitis test for subclinical mastitis detection, and all animals were deemed healthy. Cows were allowed to feed ad libitum with free access to fresh water.

2.3. Experimental design:

On day 21 before the estimated parturition date, cows were assigned into 2 groups. Group A has 18 cows that were fed an acidogenic total mixed ration (TMR; L-DCAD) (dietary cation-anion difference {DCAD} = −50 mEq/100 g of DM mEq/100 g of pre-partum matter {DM}, where DCAD = ($[Na^+]$ + $[K^+]$) – ($[Cl^-]$ + $[S^{2-}]$) based on formulations recommended by the National Research Council (NRC) for pre-partum cows (NRC, 2001; Table 1). Group B included 18 CONT cows (control) that were fed TMR without DCAD. Diets were fed three times daily (each 8 hours).

Cows were switched to a lactating cow TMR immediately after parturition based on the formulation recommended by NRC for post-partum cows (NRC, 2001). The different composition of each diet is presented in (Table 1).

Blood samples were collected between 09:00 and 11:00 with the animal restrained in a headlock. Blood samples were collected at three time periods including approximately 21 days before calving (Pre-DECAD, Pre-Diet), 3 days before calving (Pre-partum), and 3 days after calving (post-partum). Blood samples were collected from jugular/caudal tail veins into 10 mL of lithium heparin and in 10-mL K_2 EDTA evacuated tubes. Similar samples were collected from CONT cows.

2.4. Hematology analysis:

The blood tubes with K2 EDTA were used for hematological analysis. The blood samples were carefully mixed, placed on ice, and transported to the laboratory within 3 hs of collection to be analyzed using an automatic cell counter (IDEXX ProCyte Dx®; IDEXX Laboratories, Westbrook, ME, USA).

2.5. Plasma biochemical analysis:

Heparinized blood samples were transported after collection to a climate-controlled laboratory area where the plasma was harvested after centrifugation (Centerifugette 4203; ALC International Srl, Cologno Monzese, Italy) for 5 min at 3000 ×g and stored at -20°C in polypropylene vials. Plasma was thawed and used to determine total cholesterol (Chol), triglyceride (TG), urea, creatinine, glutamic-oxaloacetic transaminase (GOT), glutamate-pyruvate transaminase (GPT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) concentrations were determined spectrophotometrically (BioTek Instruments Inc., Winooski, VT, USA) at the Central Laboratory, Faculty of Veterinary Medicine, University of Benha, Egypt. Plasma cortisol concentrations were analyzed using an immunoassay (Immulite 2000 XPi; Siemens Diagnostics, Erlangen, Germany). Plasma concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) were determined using ELISA commercial kits (GenxBio Health Sciences Pvt. Ltd., Delhi, India). The concentrations of IgA and IgG were determined using commercial radial immunodiffusion (RID) kits (Rockland Immunochemicals Inc., Limerick, PA, USA).

2.6. Statistical analysis:

All data were evaluated for normal distribution or homogeneous variances. Log-transformation was used for data that deviated from normality. Data are expressed as mean ± standard deviation and $P < 0.05$ was assigned as statistically significant. Repeated-measures ANOVA was used using MIXED procedure of SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Whenever the F-test was significant, Bonferroni-adjusted P-values were used to assess differences between two treatment groups at a specific time and between times within a treatment group.

Table 1 Ingredients of the ration for DCAD diet, Lactation diet and CONT diet.

Ingredients	Kg/day (DM)	Kg/day (As-Fed)	% (DM)
DCAD diet (started 21 day before parturition)			
Corn grain, cracked	2.39	2.75	19.46
Soyabean meal, solv. 44% CP	1.81	2.00	14.72
Wheat Bran	0.89	1.00	7.24
Vitamin Premix 1	0.04	0.05	0.36
Calcium Phosphate	0.06	0.06	0.49
Salt	0.02	0.02	1.16
Alfalfa Meal, 17% CP	1.35	1.50	10.98
Beet Pulp	0.46	0.50	3.74
Vegetable Oil	0.05	0.05	0.40
Calcium Chloride	0.11	0.11	0.89
Limestone	0.16	0.16	1.27
Silage	4.95	16.50	40.26
Lactation diet (Started just after the calving)			
Corn grain, cracked	5.44	6.25	23.38
Soybean, Meal, solv.44% CP	4.16	4.60	17.90
Wheat Bran	1.29	1.45	5.55
Vitamin Premix 1	0.07	0.07	0.28
Sodium Bicarbonate	0.20	0.20	0.85
Calcium Phosphate (mono-)	0.05	0.05	0.21
Magnesium Oxide	0.05	0.05	0.21
Salt	0.09	0.09	0.38
Alfalfa meal, 17% CP	4.05	4.50	17.41
Beet Pulp	0.00	0.00	0.00
Vegetable oil	0.51	0.52	2.19
Zinc	0.01	0.01	0.03
Silage	7.35	24.50	31.60
CONT diet			
Corn grain, cracked	1.2375	1.375	16.86
Soyabean meal, solv. 44% CP	0.225	0.25	3.07
Wheat Bran	0.2975	0.35	4.05
Vitamin Premix 1	0.04	0.05	0.54
Calcium Phosphate	0.06	0.06	0.82
Salt	0.02	0.02	0.27
Alfalfa Meal, 17% CP	1.35	1.50	18.39
Beet Pulp	0.46	0.50	6.27
Vegetable Oil	0.05	0.05	0.68
Silage	3.6	12	49.05

3. RESULTS

3.1. Effect of L-DCAD diet on hematological measures

Feed acidogenic diet to cows in the pre-partum period (21 days before expected parturition) did not significantly alter the RBCs count, the PCV %, the Hb content. However, it produced marked increase in leukocytes, lymphocytes and neutrophiles (P<0.05) in pre-partum period compared to pre-DCAD and post-parturient measurements (Table 2).

Table 2 Average and standard deviation of hematological measures during pre-DECAD, pre-partum, and post-partum periods in periparturient multiparous dairy cows fed acidogenic diet (L-DCAD), and CONT diet (CONT).

Parameters	L-DCAD			CONT		
	Pre-DECAD	Pre-partum	Post-partum	Pre-diet	Pre-partum	Post-partum
Erythrocytes (10^6/mm^3)	5.9±0.2^{a}	6.2 ± 1.0^{a}	6.3±0.6^{a}	5.1±1.8^{b}	6.7±0.4^{a}	6.2±0.9^{a}
Hematocrit (%)	24.9±0.4^{a}	29.1±4.3^{a}	27.2±3.2^{a}	23.2±7.7^{a}	27.9±1.4^{a}	25.7±3.9^{a}
Hemoglobin (g/dl)	9.3±0.2^{a}	10.5±1.4^{a}	10.2±1.0^{a}	8.8±2.8^{a}	10.5±0.6^{a}	10.5±0.6^{a}
Leucocytes (10^3/mm^3)	12.6±2.1^{b*}	15.6±7.5^{a}*	13.7±4.3^{b}*	6.9±2.6^{b}	11.4±0.6^{a}	9.6±2.9^{b}
Lymphocytes (10^3/mm^3)	5.15±0.56^{a*}	7.95±5.17^{a*}	6.26±4.46^{a}*	3.3±1.26^{b}	6.1±1.9^{a}	5.6±0.8^{a}
Neutrophils (10^3/mm^3)	4.9±2.15^{a}*	5.5±2.008^{a*}	5.6±1.32^{a}*	2.7±1.8^{a}	4.2±2.3^{a}	3.06±2.2^{a}
Platelet (10^3/mm^3)	270.2±43.7^{b}*	228.5±34.9^{b}*	319.5±78.1^{a}*	336.2±138.15^{b}	390.3±121.4^{b}	466.3±52.1^{a}

$^{a-b}$Values with different letters within a row are significantly different between pre-DECAD and other time points for each type of diet (P<0.05).
* Values within raws are significantly different between same time points at different diets (P<0.05).

3.2. Effect of L-DCAD diet on immunological measures

The L-DCAD cows showed significant increments (P<0.05) in cortisol and CRP concentrations, compared to control at all periods (Table 3). Feeding DCAD diet significantly increased the IL-6 during the prepartum period only compared to pre-DCAD. The IL-6 L-DCAD cows showed significant increment (P<0.05) during the post-partum period, compared to CONT. The concentration of IgG was significantly increased after DCAD diet compared pre-DCAD. The concentrations of IgA and IgG were higher (P<0.05) in the L-DCAD cows during the post-partum period compared CONT (Table 3).

Table 3 Average and standard deviation of Plasma Cortisol, CRP, IgG, IgA, and IL6 measures during pre-DECAD, pre-partum, and post-partum periods in periparturient multiparous dairy cows fed acidogenic diet (L-DCAD), and CONT diet (CONT).

Parameters	L-DCAD			CONT		
	Pre-DECAD	Pre-partum	Post-partum	Pre-diet	Pre-partum	Post-partum
Cortisol (Miu/dl)	20.01±4.6^{b}*	36.9±7.56^{a}*	26.9±3.79^{b}*	11.25±2.24^{a}	24.8±4.29^{b}	10.24±1.0009^{a}
CRP (mg/dl)	5.7±1.7^{b}*	9.4±1.8^{a}*	8.6±0.31^{a}*	4.56±0.42^{b}	6.08±0.19^{a}	2.41±0.46^{b}
IL6 (pg/ml)	2.53±0.37^{b}	4.41±0.059^{a}*	2.015±0.32^{b}*	2.34±0.42^{b}	3.80±0.46^{a}	1.56±0.45^{b}
IgG (mg/ml)	11.3±0.73^{b*}	13.76±0.41^{a}	14.78±0.20^{a}*	13.27±1.15^{a}	13.38±0.65^{a}	13.86±0.30^{a}
IgA (mg/ml)	2.36±0.10^{b*}	2.15±0.04^{b}	4.33±0.09^{a}*	3.95±0.10^{a}	2.66±0.51^{b}	2.94±0.15^{b}

3.4. Changes in metabolites after DCAD diet

There was a significant increase (P<0.05) in TG in prepartum cows feed DCAD compared to CONT prepartum cows (Table 4). The kidney function, (urea and creatinine) were not significantly changed in cows feed DCAD diet compared to CONT (Table 4). The liver function tests showed significantly increase in GOT, GPT, GGT and ALP in cows feed DCAD compared to CONT. There was significantly increase in these enzymes in the peripartum period in both groups compared to other periods (Table 4).

Table 4 Average and standard deviation of metabolites measures during pre-DECAD, pre-partum, and post-partum periods in periparturient multiparous dairy cows fed acidogenic diet (L-DCAD), and CONT diet (CONT).

Parameters	L-DCAD			CONT		
	Pre-DECAD	Pre-partum	Post-partum	Pre-diet	Pre-partum	Post-partum
Chol (mg/ dl)	103.1±14. 9^{a}	89. 9±7.8^{b}	98.6±13.7^{a}	102.5±18.9^{a}	85.7±10.6^{b}	92.5±15.6^{a}
TG (mg/ dl)	50.4±4.3^{b*}	51.1±0.7^{b}*	53.5±1.8^{a}*	46.9±7.9^{b}	43.3±7.0^{b}	48.3±1.3^{a}
Urea (mg/dl)	37.2±1.9^{a}	37.7±6.1^{a}	35.7±5.7^{a}	30.5±2.7^{a}	36.5±2.2^{b}	33.9±4.7^{a}
Creatinine (mg/dl)	0.8±0.3^{a}	1.1±0.4^{a}	0.8±0.12^{a}	0.7±0.06^{a}	0.9±0.1^{a}	0.6±0.15^{b}
GOT(U/l)	113.0±9.5^{a}*	132.2±11.7^{a}*	71.9±5.8^{b}*	100.4±16.5^{b}	121.3±8.2^{a}	63.6±7.3^{b}
GPT(U/l)	68.2±8.5^{b*}	76.0±8.6^{a}*	61.9±11.7^{b}	60.9±3.5^{b}	65.0±10.1^{a}	60.7±1.9^{b}
GGT(U/l)	26.5±4.0^{b}*	43.8±7.6^{a}	16.7±1.4^{b}	20.9±3.6^{b}	43.5±7.5^{a}	18.6±2.9^{b}
ALK (U/l)	126.3±6.7^{b}*	144.2±8.4^{a}*	95.4±4.3^{b}*	116.8±6.8^{b}	131.0±8.4^{a}	86.0±5.5^{b}

4. DISCUSSION

The group feed acidogenic diets during prepartum period showed a significant increase in total leukocytic count (TLC) compared to CONT group during prepartum and postpartum period. Preisler et al. (2000), observed that the total leukocytes count (10^6 /ml) increased on the day of

calving. The leukocytosis observed on the day of calving might be due to the antepartum rise in cortisol (Islam et al., 2012). In acidogenic diet group showed a significant increase in lymphocyte % than CONT group during prepartum and postpartum. The neutrophil % increase during prepartum and postpartum in all groups of cows followed by a general decrease during the postpartum days. The postpartum decrease in TLC in all groups of cows are in line with Mateus et al. (2002). The increase in neutrophil % on the day of calving might have occurred due to rise in cortisol around calving day (Preisler et al., 2000).

Animals fed acidogenic diets showed a significant increase in plasma cortisol concentration compared to CONT animals. This result has been reported in earlier sheep and humans' studies, where they reported increases in cortisol secretion without changes in adrenocorticotropic hormone (ACTH) in animal or human fed mild diet-induced metabolic acidosis (Maurer et al., 2003; Espino et al., 2005). This finding is possible because acidogenic diets induce mild hypercortisolism that might play a part in metabolic-induced alterations in bone resorption (van-Staa et al., 2000; Maurer et al., 2003). The hypercortisolism-induced bone turnover is well known for several species (Hofbauer et al., 1999; Emkey et al., 2003; Weiler et al., 2003). Additionally, metabolic acidosis-induced hypercortisolism is essential, in part, for muscle mobilization associated with metabolic acidosis (Espino et al., 2005).

This study is among few studies investigating the effect of diet-induced metabolic acidosis on proinflammatory cytokines (PIC) in animals and humans. The diet-induced mild metabolic acidosis was associated with an increase in PIC around calving. Typically, PIC slightly increases around calving, possibly because parturition is the most stressful stage of the reproductive cycle of dairy cows with a high occurrence of metabolic and infectious diseases (Goff and Horst, 1997). It has been reported that activation of the PTH-vitamin D axis is associated with 3-fold increases in PIC (Heine et al., 2008). Evidence from humans also supports the fact that diet-induced metabolic acidosis is mostly associated with increases in PIC (Zahed and Chehrazi, 2017). The increased concentration of Ig in cows fed acidogenic diet after calving might be attributed the improved manipulation of dietary mineral supplementation during the prepartum period that has been shown to increase blood immunoglobulin A (IgA) and IgM in the cows, their colostrum, and their newborn calves (Roshanzamir et al., 2020).

The IL6 gene plays a crucial homeostatic role in hepatocytes during inflammation and ketosis. Both conditions are frequently experienced by cows after calving (Trevisi et al., 2005a) and in goats before kidding (Trevisi et al., 2005b). Under these conditions, IL-6 can exert important effects on metabolic and energy production pathways (Loor et al., 2007), thus contributing to the development of typical health disorders in transition cows. The IL-6 and acute phase (ceruloplasmine) response in the late pregnancy period are an important confirmation of the role of pro-inflammatory cytokinase in this period and deserve due attention. The association between IL-6 and acute phase response (APR) has been known for a long time (Baumann and Gauldie., 1994). Additionally, increases in PIC can promote B-cell differentiation into plasmablasts to secrete Ig (Heine et al., 2008).

The increased TG level in DCAD cows was explained by (Hayata et al.,2014) who found that uncompensated metabolic acidosis can induce insulin resistance and increased lipolysis.

Regarding the liver functions, the DCAD diet significantly increased Got, GPT, GGT and ALP. The increased hepatic function during the prepatum period in both groups suggest liver damage during critical transition stage. Liver damage might occur due to increased triglycerides which cause fatty liver and liver damage that caused high increase of liver enzymes, which is supported by an early investigation (West., 1990).

5. CONCLUSION

In conclusion, diet induced mild metabolic acidosis during the pre-partum period triggered immunologic and inflammatory changes that could represent periparturient additional stress to dairy cows. Therefore, the effect of addition of acidogenic diet during the critical period showed deeply studied to avoid risk factors and adverse complications.

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