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Biochemical indicators of dairy cows affected by fermentative digestive disorders

Indicadores bioquímicos de vacas leiteiras acometidas por transtornos digestivos de natureza fermentativa

Indicadores bioquímicos de vacas lecheras afectadas por trastornos digestivos de carácter fermentativo

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Abstract

The purpose of the present study was to evaluate blood metabolites in dairy cows affected by digestive disorders of fermentative nature. Sixty-six animals with clinical and laboratory diagnoses were distributed into six groups according to the diagnosis: G1 (n=5) acute ruminal acidosis; G2 (n=10) displacement of the abomasum to the right (RDA); G3 (n=16) displacement of the abomasum to the left (LDA); G4 (n=10) cecal dilation; G5 (n=6) simple indigestion; and G6 (n=19) frothy bloat. Biochemical variables related to the energy, protein, enzymatic, mineral, and hormonal profile were measured soon after diagnosis and at the time of clinical resolution. The data were submitted to analysis of variance (ANOVA) with the level of significance set at 5%. Abnormalities were found with the fermentative digestive disorders, such as a negative energy balance (NEB), liver and muscle damage, and a high level of stress. Among the conditions diagnosed, abnormalities were more evident in acute ruminal acidosis, displacement of the abomasum (RDA), and cecal dilation. The biochemical abnormalities reflected the impact caused by the digestive disorders. Thus, understanding of the dynamics of biochemical abnormalities is fundamental to the

establishment of the diagnosis, evaluation of the therapeutic response, and a more precise assessment of the prognosis, thereby avoiding greater economic losses in dairy farming activities and contributing to the improvement in the animal welfare.
Keywords: Blood metabolites; Dairy cows; Fermentative digestive disorders.

Resumo

O propósito deste estudo foi avaliar os metabólitos sanguíneos de vacas acometidas por transtornos digestivos de natureza fermentativa. Foram estudados 66 animais, distribuídos em seis grupos de acordo as enfermidades diagnosticadas clínico-laboratorialmente: G1 (n=5) acidose ruminal aguda, G2 (n=10) deslocamento de abomaso à direita (DAD), G3 (n=16) deslocamento de abomaso à esquerda (DAE), G4 (n=10) dilatação de ceco (DC), G5 (n=6) indigestão simples e o G6 (n=19) timpanismo espumoso. Foram mensuradas as variáveis bioquímicas relacionadas ao perfil energético, protéico, enzimático, mineral e hormonal, logo após o diagnóstico (MI) e no momento da resolução clínica (MF). Os dados obtidos foram submetidos à análise de variância (ANOVA) adotando nível de significância de 5%. Nos transtornos digestivos de natureza fermentativa constataram-se alterações relacionadas ao balanço energético negativo (BEN), injúria hepática e muscular, além do alto nível de estresse. Entre as enfermidades diagnosticadas, o comprometimento sistêmico foi mais evidente na acidose láctica ruminal aguda, no deslocamento de abomaso (DAD) e na dilatação de ceco. As alterações bioquímicas sanguíneas refletiram o impacto acarretado pelos distúrbios digestivos, sendo a compreensão da sua dinâmica fundamental no estabelecimento do diagnóstico, na avaliação da resposta terapêutica, assim como na avaliação mais precisa do prognóstico, evitando prejuízos econômicos à bovinocultura leiteira além de contribuir para um melhor bem estar animal.
Palavras-chave: Desordens digestivas fermentativas; Metabólitos sanguíneos; Vacas de leite.

Resumen

El propósito de este estudio fue evaluar los metabolitos sanguíneos de vacas afectadas por trastornos digestivos de naturaleza fermentativa. Se estudiaron 66 animales diagnosticados clínica y de laboratorio y divididos en seis grupos según las enfermedades diagnosticadas: G1 (n=5) acidosis ruminal aguda, G2 (n=10) desplazamiento del abomaso derecho (DAD), G3 (n=16) desplazamiento abomasal izquierdo (LAE), G4 (n=10) dilatación cecal (CD), G5 (n=6) indigestión simple y G6 (n=19) meteorismo espumoso. Las variables bioquímicas relacionadas con el perfil energético, proteico, enzimático, mineral y hormonal se midieron poco después del diagnóstico (MI) y en el momento de la resolución clínica (MF). Los datos obtenidos fueron sometidos a análisis de varianza (ANOVA) adoptando un nivel de significancia del 5%. En los trastornos digestivos de carácter fermentativo se observaron alteraciones relacionadas con el balance energético negativo (BEN), daño hepático y muscular, además de un alto nivel de estrés. Entre las enfermedades diagnosticadas, las alteraciones sanguíneas fueron más evidentes en la acidosis láctica ruminal aguda, el desplazamiento del abomaso (DAD) y la dilatación del ciego. Las alteraciones bioquímicas sanguíneas reflejan el impacto que provocan los trastornos digestivos, y el conocimiento de su dinámica es fundamental en el establecimiento del diagnóstico, en la evaluación de la respuesta terapéutica, así como en la evaluación más certera del pronóstico, evitando pérdidas económicas al ganado lechero además de contribuir a un mejor bienestar animal.
Palabras clave: Metabolitos sanguíneos; Trastornos digestivos fermentativos; Vacas lecheras.

1. Introduction

The growing world demand for proteins of animal origin (meat and milk), associated with the necessary rational and sustainable use of environmental resources, have driven the technification of dairy farming. The intensification of livestock systems, which include constant food management using high energy density diets, represents a great challenge to animal metabolism, which may interfere with homeostasis, increasing the risk of digestive and metabolic diseases (Wittwer, 2000; Van Cleef *et al*., 2009; Afonso, 2017; Coutinho *et al*., 2019; Assis *et al*., 2021).

Added to these factors, and favoring the emergence of these diseases, are the climatic seasonality conditions peculiar to some regions, such as the semi-arid region of the Brazilian Northeast. This region is characterized by periods of low rainfall, which to a certain extent lead to the supplementation of dairy cattle with low quality forage, excessive use of concentrated feed, the use of agro-industry residues of questionable nutritional quality and, in some cases, of poor digestibility, in addition to heat stress (Coutinho *et al*., 2012; Afonso, 2017).

The above factors precipitate a favorable condition for the emergence of some digestive diseases, especially those of a fermentative nature such as rumen acidosis, abomasum ectopia (displacement of the abomasum to the left -LDA and to the right -RDA), simple indigestion, cecal dilatation, and foamy bloat that require special attention due to the negative impact on

animal production (Van Cleef *et al*., 2009). It is worth mentioning that digestive disorders have been diagnosed in several different countries, including Brazil (Wittek *et al*., 2004; Cardoso *et al*. 2008; Dalto *et al*., 2009; Stengärde *et al*., 2010; Braun *et al*., 2012; Patelli *et al*., 2017; Perotta *et al*., 2018), assuming relevance in the Northeast region (Afonso *et al*., 2002; Coutinho *et al*., 2009; Câmara *et al*., 2010; Coutinho *et al*., 2012; Ribeiro *et al*., 2020; Assis *et al.*, 2021; Soares *et al*., 2021).

The use of blood biochemical variables as an auxiliary tool in the diagnosis of digestive diseases in cattle has valuable applicability, however, studies focus almost exclusively on metabolic diseases such as ketosis, fatty liver, ruminal lactic acidosis, displacement of the abomasum (DA), and those that are mechanical in nature, and it is known that the information resulting from blood biochemistry allows better understanding of the dynamics of these diseases, providing useful information for diagnosis, treatment, and prevention (Wittek *et al*., 2004; Stengärde *et al*., 2010; Grosche *et al*., 2012; Maden *et al*., 2012; Coutinho *et al*., 2019; Santos *et al*., 2020). Given the economic impact on dairy farming resulting from digestive diseases, combined with better systemic understanding of these disorders, the current work aimed to study the blood biochemical indicators of dairy cows affected by digestive diseases of a fermentative nature.

2. Material and methods

2.1 Ethics committee

This work received a favorable opinion from the Ethics Committee on the Use of Animals (CEUA), from the Federal Rural University of Pernambuco under license no. 035/2018 CEPE/UFRPE, according to the norms of the Brazilian College of Animal Experimentation (COBEA) and *National Institute of Health Guide for Care and Use of Laboratory Animals*.

2.2 Location

The work was carried out at the facilities of the Clínica de Bovinos de Garanhuns, Garanhuns-PE *Campus*, Universidade Federal Rural de Pernambuco (CBG/UFRPE).

2.3 Animals

Sixty-six crossbred dairy cows were evaluated, reared semi-intensively, calved for at least two months and affected by different digestive diseases of a fermentative nature. The animals were submitted to clinical and laboratory exams (Dirksen *et al*., 1993; Kaneko *et al*., 2008) and after diagnosis they were divided into six groups based on the primary diagnosis: G1 (n=05) Ruminal acidosis, G2 (n=10) right displaced abomasum - RDA, G3 (n=16) left displaced abomasum - LDA, G4 (n =10) cecal dilation, G5 (n=06), simple indigestion, and G6 (n=19) foamy bloat. It should be pointed out that 43% of the animals had diseases concomitant with digestive disorders, such as pneumonia (10.76%), mastitis (9.23%), pododermatitis (7.69%), metritis (4.61%), reticulitis (4.61%), abomasal ulcer (3.07%), and bovine hemoparasitosis (3.07%). All the animals remained hospitalized at the CBG/UFRPE, where they were treated daily and clinically followed up until the final resolution, of these 91% (60/66) were clinically discharged, 4.5% (3/66) were euthanized, 3% (2 /66) died, and 1.5% (1/66) were sent for slaughter.

2.4 Observation moments

The established evaluation moments were the day when the animal was admitted to the hospital unit and the clinical diagnosis defined (Initial Moment - MI) and, later, at the moment of clinical resolution (Final Moment - MF), which may be hospital discharge, indication of slaughter, indication of euthanasia, or natural death.

2.5 Collection and storage of samples

Blood samples were collected by jugular puncture with 25x8mm needles in vacutainer® tubes, without anticoagulant (serum collection) for blood analysis. For determination of glucose and L-lactate, samples were collected in tubes containing sodium fluoride/K3EDTA (obtaining plasma). Serum and plasma samples were placed in polyethylene tubes (Eppendorf type) and stored in an ultrafreezer[1] (-80ºC), for subsequent laboratory analysis.

2.6 Laboratory processing:

The variables representing the energy (non-esterified fatty acids - NEFAs[2], β-hydroxybutyrate - BHB [3], glucose[4], triglycerides[5], and cholesterol[6]), protein (total protein - PT[7], albumin[8], globulin, urea[9], and creatinine[10]), enzymatic (gamma glutamyltransferase - GGT [11], aspartate aminotransferase - AST [12], glutamate dehydrogenase - GLDH [13], creatine kinase - CK [14], and L-lactate [15]), mineral (total calcium - CaT [16], ionized calcium – Ca^{++}, and phosphorus - P[17]), and hormonal profile (cortisol [18] and insulin[19]) were measured. With the exception of hormones, which were read by chemiluminescent immunoassay[20], the other variables were processed in a semi-automatic biochemical analyzer [21]. Ionized calcium was determined according to the formula: Ca^{++}= 6 x CaT - [(0.19 x PT) + Alb. / 3] / (0.19 x PT) + Alb. + 6 (Cesco *et al*., 2004).

2.7 Statistical analysis

The data are described using means and standard error of the mean. Subsequently, they were tested for distribution, using the Kolmogorov-Smirnov test. Those which did not meet the normality assumptions were subjected to transformation with a logarithmic basis (LogX+1) or by the square root [SR (x=1/2)]. The data that met the assumptions of normality and the transformed data were subsequently subjected to analysis of variance (Test F), with a significance level of 5%, separated as causes of variation into the effects of the groups (G1, G2, G3, G4, G5, and G6) and moments at the diagnosis (MI) and clinical resolution (MF) moments. As this is an experiment with entirely random clusters, the aim was to investigate the effects and interactions between them. When there was significance in the F test, the means were compared by the minimum significant difference (m.s.d.) of the Student-Newman-Keuls test. Data were analyzed using the computer program Statistical Analysis-System (SAS, 2009).

[1]-Ultralow freezer NuAire Inc., 2100 Fernbrook Lane N. Plymouth, MN 55447, USA.
[2]-AGNEs - Randox Laboratories Ltd, Ardmore, Diamond Road, Crumlin, Antrim, BT 29 4QY, UK
[3]-BHB - Randox Laboratories Ltd, Ardmore, Diamond Road, Crumlin, Antrim, BT 29 4QY, UK
[4]-Glucose PAP – Labtest Diagnóstica S.A., Av. Paulo Ferreira da Costa 600, Lagoa Santa, MG 334000-000, Brasil
[5]-Tryiglicerides Liquiform - Labtest Diagnóstica S.A.
[6]-Cholesterol Liquiform - Labtest Diagnóstica S.A.
[7]- Total Protein - Labtest Diagnóstica S.A.
[8]-Albumin - Labtest Diagnóstica S.A.
[9]-Urea CE - Labtest Diagnóstica S.A.
[10]-Creatinine - Labtest Diagnóstica S.A.
[11]-Gama GT Liquiform - Labtest Diagnóstica S.A.
[12]- Liquiform AST - Labtest Diagnóstica S.A.
[13]-GLDH – Diasys Deutschland
[14]-CK-NAC Liquiform - Labtest Diagnóstica S.A.
[15]- Enzymatic lactate - Labtest Diagnóstica S.A.
[16]- Liquiform Calcium - Labtest Diagnóstica S.A.
[17]- Liquiform Phosphorus UV - Labtest Diagnóstica S.A.
[18]-Access Immunoassay Systems Cortisol – Beckman Counter® Calçada Aldebarã 39 – Alphaville, 06541-055, Brasil
[19]-Access Immunoassay Systems Ultrasensitive Insulin – Beckman Counter®
[20]-Quimioluminescência Beckman Counter, Inc.
[21]-Labquest - Labtest Diagnóstica S.A.

3. Results

3.1 Biochemical energy indicators

Serum levels of NEFAs at MI were significantly higher (P<0.05) in relation to MF, however, they did not differ between the disease groups (Tables 1 and 2). At MI, the mean values of BHB in the group of animals with ruminal acidosis were significantly elevated (P=0.0164) in relation to the other groups. At MF, all groups presented BHB values within the normal range for the species, with a significantly lower reduction in the group of animals with ruminal acidosis compared to MI (P=0.0142) (Tables 1 and 2).

Plasma glucose values were significantly higher (P=0.0027) in the group of animals with RDA when compared to the other groups. Blood glucose values at MI were significantly higher than at MF (P<.0001) (Tables 1 and 2).

Mean concentrations of triglycerides were not affected by group (P=0.061) or moment (P=0.091), however cholesterol values were significantly higher in the group of animals with ruminal acidosis (P<.0001) in relation to the other groups of diseases, and these values were higher (P<0.0385) at MI in relation to MF (Tables 1 and 2).

3.2 Protein biochemical indicators

Analyzing the behavior of PT, the highest values were found in the group of animals with ruminal acidosis and the lowest in the group of animals with RDA, with a significant difference between them (P=0.0063). The mean values found at MI were significantly higher (P<0.0114) in relation to MF. The albumin concentration was higher in the group of animals with ruminal acidosis (P=0.0075) in relation to the animals with LDA, cecal dilation, and simple indigestion. There was also a significant reduction in this variable at MF (P=0.0011). For globulin, the lowest value was obtained in the group of animals with RDA, with a significant difference from the other groups of diseases (P=0.0033). There was no moment effect (Tables 1 and 3).

In animals affected by ruminal acidosis and RDA the mean values of urea (67.45 mg/dL and 61.49 mg/dL, respectively) were significantly higher (P=0.0015) in relation to animals with LDA (25.49 mg/dL). Considering the moments, the mean concentrations were higher at MI, with a difference from MF (P<.0001). Regarding the creatinine concentration in the group of animals with ruminal acidosis, a significant difference (P<.0001) was verified in relation to the other groups of diseases. There was also a moment effect, in which the result obtained for this variable at MI was higher (P=0.0286) than at MF (Tables 1 and 3).

Evaluating the serum activity of L-Lactate, a group effect was found, highlighting significantly more expressive values (P=0.0274) in the groups of animals with cecal dilation, RDA and foamy bloat, in relation to the other groups. In the analyzed moments, there was also a significant difference (P<.0001) with activity greater at M1 than MF (Tables 1 and 4).

3.3 Enzymatic indicators

The serum activity of GGT in the group of animals with RDA was higher, with a difference from the groups of animals affected by cecal dilation and foamy bloat (P=0.0074). However, there was no significant difference between the moments (P=0.2459). Serum AST activity was significantly higher (P=0.0261) in the group of animals with simple indigestion compared to the other groups, except for animals affected by LDA, with no moment effect (P=0.3328). There was no significant difference in the values of serum activity of GLDH between the groups (P=0.0627) of diseases at the two analyzed moments (P=0.1248); however, at both moments its activity was higher than the normal limits for the species (Tables 1 and 4).

The highest value of serum CK activity was observed in the groups of animals affected by simple indigestion and RDA, with a difference (P=0.0006) from the other groups of diseases. At the analyzed moments, CK showed significantly higher serum activity (P= 0.0127) at MI, in relation to MF (Tables 1 and 4).

3.4 Mineral and hormonal biochemical indicators

Serum concentrations of CaT and Ca++ were significantly lower in the group of animals with cecal dilation than in the group of animals affected by simple indigestion (P=0.0071). With respect to the analysis of this mineral at the time of observation, there was no difference in the levels of CaT (P=0.4086), however, the levels of Ca++ obtained at the time of diagnosis were significantly lower (P=0.0479) in relation to the values at the time of clinical resolution. In the groups of animals with LDA and cecal dilation, phosphorus levels were significantly lower (P=0.0144) in relation to the group of animals with ruminal acidosis. Between the moments, MI and MF, there was no significant difference (P=0.6236) in the levels of this mineral (Tables 1 and 5).

Analyzing the hormonal profile related to insulin, it was found that values did not change significantly between the disease groups (P=0.5467); however, in the MF, the mean values were significantly (P<.0001) lower than in the MI (Tables 1 and 5). Regarding the dynamics of cortisol, an interaction was found (P=0.05), where in the MI, the group of animals with cecal dilation was highlighted, presenting significantly higher mean concentrations in relation to the groups of animals diagnosed with ruminal acidosis, LDA and simple indigestion (P=0.0065). Analyzing the behavior of this variable between the moments, it was verified that, at MF, there was a significant reduction (P<.0001) in the values of the groups of animals with RDA, LDA, cecal dilation, and foamy bloat, in relation to MI (Tables 1 and 5).

Table 1. Significance level (Pr>F) of the variation factors (groups, moments, and interactions) of the analysis of variance of biochemical blood energy, protein, enzymatic, hormonal, and mineral indicators of dairy cows (n=66) affected by fermentative digestive disorders at the time of diagnosis and clinical resolution.

Biochemical indicators	Variance factors (Pr>F)		
	Group	Moments	G x M
	Blood serum		
β- hydroxybutyrate (mmol/L)	0.0164	0.0142	<.0001
NEFAs (mmol/L)	0.4039	<.0001	0.7822
Glucose (mg/dL)	0.0027	<.0001	0.0895
Cholesterol (mg/dL)	<.0001	0.0385	0.9285
Triglycerides (mg/dL)	0.0610	0.0906	0.5018
Total Protein (g/dL)	0.0063	0.0114	0.9103
Albumin (g/dL)	0.0075	0.0011	0.9721
Globulin (g/dL)	0.0032	0.1911	0.8770
Urea (mg/dL)	0.0015	<.0001	0.3765
Creatinine (mg/dL)	<.0001	0.0286	0.9277
AST (U/L)	0.0261	0.3328	0.1045
GGT (U/L)	0.0074	0.2459	0.5882
GLDH (U/L)	0.0627	0.1248	0.1449
CK (U/L)	0.0006	0.0127	0.0600
L-Lactate (mg/dL)	0.0274	<.0001	0.2972
Insulin (pmol/L)	0.5467	<.0001	0.3828
Cortisol (nmol/L)	0.0065	<.0001	0.1453
Total Ca (mg/dL)	0.0099	0.4086	0.9637
Ionized Ca (mmol/L)	0.0071	0.0479	0.9295
Phosphorus (mg/dL)	0.0144	0.6236	0.4928

Source: Authors - Garanhuns Bovine Clinic, Federal Rural University of Pernambuco (2022).

Table 2. Mean and standard error of the mean values of biochemical blood energy indicators of dairy cows (n=66) affected by fermentative digestive disorders at the time of diagnosis (MI) and clinical resolution (MF).

	NEFAs (mmol/dL)			BHB (mmol/dL)		Glucose (mg/dL)			Triglycerides (mg/dL)			Cholesterol (mg/dL)		
Groups	MI	MF	MG	MI	MF	MI	MF	MG	MI	MF	MG	MI	MF	MG
G1	0.68±0.16	0.45±0.09	0.56^{A}	$1.48±0.46^{Aa}$	$0.24±0.07^{Ab}$	55.86±9.97	45.20±3.19	50.53^{B}	20.16±3.40	16.82±1.98	18.49^{A}	210.90±44.31	202.60±41.10	206.75^{A}
G2	1.03±0.12	0.53±0.14	0.78^{A}	$0.52±0.08^{Ba}$	$0.52±0.03^{Aa}$	132.22±25.17	56.89±6.07	90.06^{A}	20.94±2.58	15.88±0.90	18.40^{A}	107.24±12.42	87.79±11.39	97.52^{B}
G3	0.84±0.15	0.39±0.08	0.62^{A}	$0.60±0.08^{Ba}$	$0.42±0.04^{Aa}$	64.09±3.56	48.95±1.47	56.28^{B}	14.95±1.04	15.14±0.99	15.05^{A}	84.78±7.87	78.45±5.60	81.61^{B}
G4	0.77±0.15	0.38±0.09	0.58^{A}	$0.40±0.04^{Ba}$	$0.47±0.08^{Aa}$	72.21±9.47	53.27±4.21	62.74^{AB}	14.58±1.24	14.33±1.18	14.45^{A}	96.32±8.79	84.39±11.51	90.35^{B}
G5	0.72±0.27	0.32±0.10	0.50^{A}	$0.47±0.16^{Ba}$	$0.56±0.14^{Aa}$	66.01±10.62	48.99±2.55	57.50^{B}	13.39±1.85	14.31±1.12	13.89^{A}	112.02±24.53	89.16±16.48	99.55^{B}
G6	0.68±0.11	0.47±0.08	0.58^{A}	$0.47±0.09^{Ba}$	$0.41±0.05^{Aa}$	91.13±9.56	49.11±1.71	69.55^{AB}	19.23±1.80	17.04±1.06	18.13^{A}	142.38±18.32	110.95±14.90	126.67^{B}
MG	0.79	0.43				81.74	50.57		17.35	15.72		118.64	100.50	
P	a	b				a	b		a	a		a	b	

* Different lowercase letters on the same line differ statistically from each other (P<0.05) characterizing a moment effect.
* Different lowercase letters on the same column differ statistically from each other (P<0.05) characterizing a group effect.
Source: Authors - Garanhuns Bovine Clinic, Federal Rural University of Pernambuco (2022).

Table 3. Mean and standard error of the mean values of biochemical blood protein indicators of dairy cows (n=66) affected by fermentative digestive disorders at the time of diagnosis (MI) and clinical resolution (MF).

	Total protein (g/dL)			Albumin (g/dL)			Globulin (g/dL)			Urea (mg/dL)			Creatinine (mg/dL)		
Groups	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF	MG
G1	8.77±0.18	8.41±0.21	8.59^{A}	2.80±0.15	2.59±0.18	2.69^{A}	5.97±0.29	5.81±0.20	5.89^{A}	70.30±34.31	64.60±37.27	67.45^{A}	2.87±1.41	3.01±1.88	2.94^{A}
G2	7.25±0.73	6.45±0.31	6.85^{C}	2.61±0.23	2.16±0.13	2.38^{AB}	4.64±0.52	4.29±0.25	4.46^{B}	90.08±27.83	32.91±7.38	61.49^{A}	1.90±0.49	1.08±0.17	1.49^{B}
G3	7.94±0.31	7.49±0.32	7.71^{ABC}	2.24±0.12	1.99±0.07	2.12^{B}	5.69±0.34	5.49±0.36	5.59^{A}	29.35±4.03	21.63±1.85	25.49^{B}	1.02±0.09	0.76±0.03	0.89^{B}
G4	7.48±0.35	7.17±0.34	7.32^{BC}	2.22±0.15	1.82±0.11	2.02^{B}	5.27±0.30	5.35±0.30	5.30^{A}	47.84±11.26	34.69±9.10	41.27^{AB}	1.12±0.11	0.94±0.10	1.03^{B}
G5	8.24±0.62	8.14±0.58	8.18^{AB}	2.20±0.23	1.93±0.17	2.05^{B}	6.04±0.65	6.21±0.71	6.13^{A}	56.23±12.76	24.19±4.71	38.75^{AB}	1.46±0.24	1.16±0.19	1.30^{B}
G6	8.32±0.33	7.41±0.23	7.86^{ABC}	2.42±0.13	2.16±0.15	2.29^{AB}	5.90±0.31	5.24±0.19	5.57^{A}	53.93±7.58	29.08±2.10	41.51^{AB}	1.35±0.14	0.99±0.06	1.17^{B}
MG	7.96	7.39		2.38	2.08		5.57	5.30		53.94	30.95		1.44	1.11	
P	a	b		a	b		a	a		a	b		a	b	

* Different lowercase letters on the same line differ statistically from each other (P<0.05) characterizing a moment effect.
* Different lowercase letters on the same column differ statistically from each other (P<0.05) characterizing a group effect.
Source: Authors - Garanhuns Bovine Clinic, Federal Rural University of Pernambuco (2022).

Table 4. Mean and standard error of the mean values of biochemical blood enzymatic indicators of dairy cows (n=66) affected by fermentative digestive disorders at the time of diagnosis (MI) and clinical resolution (MF).

	GGT (U/L)			AST (U/L)			GLDH (U/L)			CK (U/L)			L-Lactate (mg/dL)		
Groups	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF	MG
G1	45.90±15.30	38,45±4,42	41,31^{AB}	54,48±5,13	115,24±46,80	84,86^{B}	40,79±16,28	73,66±25,62	57,23^{A}	126,28±23,54	127,49±34,89	126,89^{B}	8,91±2,44	6,14±0,23	7,52^{B}
G2	68.09±11.60	53,08±10,00	60,59^{A}	132,56±31,02	117,34±24,11	124,93^{AB}	48,56±16,29	44,69±30,21	46,63^{A}	1073,43±352,60	356,98±75,76	715,21^{A}	29,17±8,93	8,06±3,15	18,62^{A}
G3	44.46±8.44	61,71±17,71	52,81^{AB}	106,72±17,06	83,15±8,12	94,94^{B}	35,27±8,76	41,30±10,29	38,29^{A}	349,15±125,82	144,20±27,28	246,67^{B}	11,58±1,95	7,06±0,80	9,25^{B}
G4	31.36±1.37	33,66±3,64	32,51^{B}	59,19±4,75	104,24±7,63	81,71^{B}	9,57±1,49	32,01±12,53	20,79^{A}	182,13±59,73	393,42±70,82	287,78^{B}	31,58±13,23	9,48±2,83	20,53^{A}
G5	34.42±5.50	35,70±4,27	35,06^{AB}	149,81±68,10	155,39±57,23	152,86^{A}	23,02±4,83	79,95±30,43	50,99^{A}	1096,77±642,19	554,49±245,04	825,63^{A}	15,24±4,94	4,55±0,33	9,90^{B}
G6	32.21±5.18	39,86±5,35	36,04^{B}	79,94±6,78	81,88±11,67	80,91^{B}	30,96±6,84	37,28±16,68	34,12^{A}	354,87±85,49	155,93±21,20	255,40^{B}	24,57±4,50	7,40±0,87	15,75^{A}
MG	41.53	45,71		94,85	100,16		31,79	45,33		530,44	288,75		21,24	7,38	
P	a	a		a	a		a	a		a	b		a	b	

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* Different lowercase letters on the same line differ statistically from each other (P<0.05) characterizing a group effect.
Source: Authors - Garanhuns Bovine Clinic, Federal Rural University of Pernambuco (2022).

Table 5. Mean and standard error of the mean values of biochemical blood mineral and hormonal indicators of dairy cows (n=66) affected by fermentative digestive disorders at the time of diagnosis (MI) and clinical resolution (MF).

	Total calcium (mg/dL)			Ionized Calcium (mmol/L)			Phosphorus (mg/dL)			Insulin (pmol/L)			Cortisol (nmol/L)	
Groups	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF	MG	MI	MF
G1	7.54±0.36	8.01±0.19	7.78^{AB}	1.07±0.06	1.16±0.03	1.11^{AB}	7.73±1.44	8.48±1.55	8.10^{A}	6.75±2.55	7.68±3.86	7.27^{A}	$51.52±12.99^{Ba}$	$94.92±83.07^{Aa}$
G2	7.70±0.65	7.92±0.30	7.81^{AB}	1.13±0.07	1.25±0.04	1.19^{AB}	7.62±1.27	5.48±0.75	6.55^{AB}	10.1±3.56	3.56±0.71	6.83^{A}	$318.09±126.96^{ABa}$	$23.15±7.65^{Ab}$
G3	6.96±0.35	7.03±0.49	7.00^{AB}	1.05±0.05	1.10±0.08	1.07^{AB}	5.26±0.42	4.71±0.47	4.99^{B}	11.30±2.43	2.54±0.25	6.92^{A}	$81.69±18.15^{Ba}$	$38.54±13.01^{Ab}$
G4	6.53±0.31	6.36±0.52	6.45^{B}	1±0.04	1.1±0.07	1.00^{B}	5.15±0.49	5.98±0.58	5.57^{B}	4.62±1.17	5.35±2.02	4.98^{A}	$371.39±88.95^{Aa}$	$68.65±26.66^{Ab}$
G5	7.92±0.33	8.79±0.32	8.39^{A}	1.19±0.02	1.37±0.05	1.28^{A}	6.53±0.84	6.41±0.80	6.47^{AB}	12.08±5.64	2.26±0.43	7.61^{A}	$77.57±22.17^{Ba}$	$79.12±24.86^{Aa}$
G6	7.08±0.52	7.13±0.30	7.11^{AB}	1.05±0.07	1.10±0.05	1.07^{AB}	6.25±0.69	6.06±0.50	6.16^{AB}	20.05±9.40	4.42±0.90	12.46^{A}	$225.94±51.07^{ABa}$	$27.52±3.86^{Ab}$
MG	7.16	7.33		1.08	1.17		6.18	5.87		12.32	4.04			
P	a	a		b	a		a	a		a	b			

* Different lowercase letters on the same line differ statistically from each other (P<0.05) characterizing a moment effect.
* Different lowercase letters on the same line differ statistically from each other (P<0.05) characterizing a group effect.
Source: Authors - Garanhuns Bovine Clinic, Federal Rural University of Pernambuco (2022).

4. Discussion

4.1 Energy indicators

In the current work, the high serum levels of NEFAs at MI in all groups of diseases reflect the condition of a high negative energy balance (NEB) due to the reduction in food intake observed in the animals as a result of their respective digestive diseases, thus not supplying the required energy demand. However, only the group of animals diagnosed with acute ruminal acidosis showed high levels of BHB, characterizing a condition of secondary ketosis, and it is likely that the severity of the clinical condition found in cases of acute ruminal acidosis justifies this result (Nagaraja & Lechtenberg, 2007).

Studies show that NEFAs are a sensitive indicator of energy balance in cows (Herdt, 2000) and their increased blood concentrations have been correlated with DA and ketosis, among other peripartum diseases (Cardoso *et al*., 2008; Stengärde *et al*., 2010; Seifi *et al*., 2011; Dokovic *et al*., 2012; Khalphallah *et al*., 2015; Ribeiro *et al*., 2020). LeBlanc *et al*. (2005), also highlighted that the increase in serum concentrations of NEFAs and BHB in the first postpartum week was associated with a higher risk of subsequent DA. This condition was also observed by Brown *et al*. (2000), studying confined cattle affected by ruminal acidosis, who justified the increase in NEFAs by the reduction in dry matter intake. The concentrations of NEFAs and BHB within the normal limits for the species verified at MF, are due to the adequate adoption of therapeutic measures, with consequent clinical recovery and restoration of negative energy balance, a similar condition to that observed in other studies (Brown *et al*., 2000; Antanaitis *et al*., 2014; Khalphallah *et al*., 2015; Perotta *et al*., 2018; Ribeiro *et al*., 2020).

Glucose concentrations at MI were significantly higher and above the normal range for the species (hyperglycemia), which was more pronounced in the group of animals affected by right displaced abomasum. High blood glucose values compatible with those of the current work were also observed in dairy cows equally affected by abomasal displacement (Dezfouli *et al*., 2013; Rawashdeh *et al*., 2017; Ribeiro *et al*., 2020). For Van Meirhaege *et al*. (1988) and Zadnik (2003), hyperglycemia may be associated with a decreased flow of pancreatic juice and disturbance of blood circulation in the parenchyma of this organ, due to changes in duodenal and omental position that occur during cases of DA, thus generating failure in the tissue response to insulin, which exerts a glycolytic function. Furthermore, the increase in serum glucose can also be explained by the increase in cortisol levels in these animals, since this hormone has gluconeogenic action, stimulating the release of amino acids from peripheral tissues and inducing the synthesis of key enzymes to carry out the same activity, in addition to an inhibitory action on insulin, by providing a reduction in peripheral receptor activity and, consequently, decreasing the ability of tissues to use glucose (Sapolsky *et al*., 2000; Schlumbohm, 2008). Different results were reported by other authors who found conditions of hypo and normoglycemia associated with a condition of ketosis and low food consumption (Antanaitis *et al*., 2014; Khalphallah *et al*., 2015; Patelli *et al*., 2017; Perotta *et al*., 2018). The difference between the hyperglycemic state at MI and the normoglycemic condition at MF, in the animals with the different types of disorders studied, can be justified by the level of stress that the animals were in at the time of diagnosis, confirmed by the high values found for serum cortisol (Kaneko *et al*., 2008), as well as the condition of clinical recovery at MF, causing the biochemical indicators to return to physiological limits (Coutinho *et al*. 2019).

The significant increase (P<.0001) in serum cholesterol values in the group of animals with ruminal acidosis in relation to the other groups of diseases was significant and this condition may be related to the increase in triglyceride synthesis in the liver based on the concentration of NEFAs, which is likely to reflect the condition of serum cholesterol, and the low production of lipoproteins (VLDL, LDL, and HDL) (Grummer, 1993). However, divergent results reveal low serum values of this variable in cattle with digestive disorders (Brown, 2000; Santos *et al*., 2020), which may be associated with the occurrence of liver diseases (Ashmawy, 2015). The reduction observed in the values of this variable at MF is probably linked to the improvement in the clinical condition due to the established therapy for the diseases studied.

Blood triglyceride values were within normal limits for the species (Pogliani *et al*., 2007), not differing between the diseases during the analyzed moments. A study also carried out in the same region as the current study identified similar behavior of this variable, when analyzing it in the blood and peritoneal fluid of cattle affected by intestinal disorders and reticulitis (Santos *et al*., 2020). However, Van Den Top *et al*. (2005), found a reduction in the plasma concentration of triglycerides in the postpartum period, being more pronounced in cows with hepatic steatosis. González *et al*. (González *et al*., 2009) also reported a lower serum concentration of triglycerides in cows with high values of BHB and NEFAs, as a consequence of excess fatty acids that are mobilized to the liver to be used as an energy source; and the limited hepatic capacity to export triglycerides as VLDL results in their deposition within the hepatocytes, with a consequent reduction in their serum concentration.

4.2 Protein indicators

The higher average concentrations for PT and albumin observed in the group of animals affected with ruminal acidosis in relation to the other groups of diseases, can be explained by the clinical framework of dehydration, characteristic in the acute form of this disease (Nagaraja & Lechtenberg, 2007; Ortolani *et al*., 2010; Meyer *et al*., 2017; Soares *et al*., 2018). Other groups in this work did not show changes in PT values. However, Cardoso *et al*. (2008) and Patelli *et al*. (2017) reported significantly lower serum PT levels, but within the normal range, in DA cows, and attributed this condition to feed restriction due to the condition.

Regarding hypoalbuminemia, with the exception of the group of acute ruminal acidosis, in all other groups it may be related to the decrease in hepatic synthesis during inflammatory processes, due to the prioritization of acute phase protein synthesis (Cray et al. 2009), in the presence of concomitant diseases, as observed in this study or in situations of liver injury (Sevinc *et al*., 2002; Aslan *et al*., 2003; Assis *et al*., 2021, this hypothesis being ratified in this study by the high values of serum GLDH and GGT activity. Another hypothesis would be associated with abdominal disorders, which can trigger increased vascular permeability, resulting from circulatory impairment and consequent extravasation of this protein into the cavity (Santos *et al*., 2020). The momentum effect that resulted in the reduction of serum total protein concentration is justified by hydroelectrolytic therapy.

Despite the significant reduction in globulin concentration in the group of animals with RDA in relation to the other groups of diseases, the hyperglobulinemia observed at both moments in the other groups stands out. This is probably due to the antigenic stimuli of the diseases that co-occurred (pneumonia, mastitis, pododermatitis, metritis, reticulitis, abomasal ulcer and bovine parasitic sadness) and digestive disorders, diagnosed in 43% of the animals. A framework of hyperglobulinemia similar to that of the current study was also evidenced in dairy cattle affected by intestinal disorders and traumatic reticulitis (Santos *et al*., 2020; Assis *et al*., 2021). Similar findings were also found by Stengärde *et al*. (2010), Khalphallah *et al*. (2015), and Patelli *et al*. (2017), who reported that, respectively, 72%, 64%, and 30.7% of the cows they studied with DA had at least one concomitant disease, such as retained placenta, endometritis/metritis, ketosis, hypocalcemia, laminitis, mastitis, and abomasal tumor, among others.

The high levels of urea and creatinine observed in the group of animals diagnosed with ruminal acidosis characterize the condition of pre-renal azotemia and, probably, occurred due to the effective reduction in renal blood perfusion, due to dehydration (Underwood, 1992; Ortolani *et al*., 2008). Other studies have reported similar cases of azotemia in cattle affected by digestive diseases (Cardoso *et al*., 2008; Braun *et al*., 2012; Dezfouli *et al*., 2013; İssi *et al*., 2016). However, AL-Rawashdeh *et al*. (2017) found no significant alterations in serum urea and creatinine concentrations in cows affected by DA.

The reduction in the values of these variables, between the moments, was due to hydroelectrolytic reestablishment after the implementation of the therapy, despite the values being within the normal range for the species.

4.3 Enzymatic indicators

The increase in the activities of liver enzymes, especially GLDH and GGT, in greater intensity in the group of animals with RDA, indicates liver injury that persisted between the analyzed moments. These findings are in agreement with earlier studies in cows with DA and hepatic lipidosis (Zadnik, 2003; Stengärde *et al*., 2010; Maden *et al*., 2016); since these enzymes (especially GLDH) depict, with greater reliability and specificity, hepatic injuries in cattle (Noro *et al*., 2013).

Serum CK activity above the normal limits that was more expressive (P=0.0006) in the groups of animals with RDA and simple indigestion, together with a greater magnitude at the MI moment (P=0.0127), reflect tissue damage that can be attributed to excessive distension of the organ wall (mainly abomasum and cecum), when dilated and/or twisted. It is also necessary to consider the effect of the use of medications, of a parenteral nature, performed before the hospitalization of these animals, as well as the prolonged decubitus due to the diseases. Maden *et al*. (2012) and Ribeiro *et al*. (2020) also found a significant increase in serum CK activity in cattle with right abomasum displacement, associating it with organ wall damage. In a recent study, Santos *et al*. (2020) also found elevation in the serum activity of CK of cows affected by intestinal disorders and reticulitis, in both the serum and the peritoneal fluid of these animals.

The increase in plasma values of L-Lactate at the MI moment of the groups of animals affected by right abomasal displacement, cecal dilation, and foamy bloat may be related to dehydration and damage to the organ walls when they are intensely distended. It is known that hyperlactatemia occurs in cases of severe dehydration or hypovolemic shock, septic shock, and other conditions that reduce tissue perfusion, leading to ischemia and necrosis, since, once tissue hypoxia is installed, the pathway for obtaining anaerobic energy is activated and this is one of the metabolites produced (Russell & Roussel, 2007; Allen & Holm, 2008). In cows with abomasal volvulus Wittek *et al*. (2004) found that decreased perfusion of the abomasal wall is accompanied by local synthesis of L-lactate as a result of anaerobic glycolysis. In agreement with the results of the current work, increases in L-lactate were detected in the blood and peritoneal fluid of cattle with intestinal disorders, reticulitis, and abomasopathies (Grosche *et al*., 2012; Santos *et al*., 2020; Ribeiro *et al*., 2020). The reduction in L-lactate values at MF indicates the repair of dehydration and, consequently, tissue reperfusion as a function of the therapy employed, reflecting the improvement in the clinical condition.

4.3 Mineral and hormonal indicators

The difference in the levels of Ca++, between the moments studied can be explained by the clinical condition of the animals affected by the different disorders, in which the condition of food intake was compromised. However, the values found for this mineral do not confirm the existence of hypocalcemia, although they remained at the lower limit of the normal range in some groups of diseases in this study. According to Boink *et al*. (1991) measurement of Ca++ is the gold standard analysis to be used in the interpretation of this metabolite, since this is the physically active form and most important for immediate metabolic function.

The significant difference between the Ca++ levels of the group of animals diagnosed with cecal dilation and the group of animals with simple indigestion can be explained by the greater severity of the impairment in gastrointestinal function, in addition to the degree of inappetence/anorexia observed in cases of cecal dilation, with consequent impairment in calcium absorption (Daniel, 1993; Goff, 2008). In other studies, low levels of calcium were reported in cows affected by LDA, RDA, abomasal torsion, and cecal dilation (Zadnik, 2003; Chapinal *et al*., 2011; Seifi *et al*., 2011; Braun *et al*., 2012; Al-

Rawashdeh *et al*., 2017; Patelli *et al*., 2017). Seifi *et al*. (2011) highlighted that cows with a total calcium concentration of less than 2.2 mmol/L are more prone to DA.

Serum phosphorus levels, despite being lower in the groups of animals with LDA and cecal dilation (P=0.0144), still remained within the normal limits for the species. These results are in agreement with those found by Dezfouli *et al*. (2013) who also reported normal levels of this mineral in cows with left abomasal displacement. However, low serum phosphorus levels in cows affected by abomasal displacement, cecal dilation, and ruminal acidosis were attributed to reduced feed intake (Brown *et al*., 2000; Delgado-Lecaroz *et al*., 2000; Patelli *et al*., 2017).

The differences found between MI (high values) in relation to the MF can be justified by the stimuli arising from the hyperglycemia also observed in the animals of this work. Similar findings were observed by Ribeiro *et al*. (2020) in cows with abomasal displacement; additionally, for Van Meirhaeghe *et al*., in animals with this disorder, changes in the production of fatty acids, butyrate and valerate, and other insulinogenic substances may stimulate an insulin response superior to that produced by glucose, and therefore, hyperinsulinemia may be related to the pathogenesis of this paratopia. Conflicting results were reported by Khalphallah *et al*. (2015) who did not find significant variations in insulin concentrations in cows with abomasum displacement. In contrast, low insulin concentrations in animals with abomasal displacement were attributed to the reduction in food intake caused by the disease, and consequent low stimulus for its production and secretion (Agenäs *et al*., 2003; Stengärde *et al*., 2010).

The higher values for cortisol in the groups of animals with cecal dilation and RDA are probably due to a greater stress condition in the animals affected by these disorders, and, as previously discussed, may have directly contributed to the hyperglycemia condition verified in this work, at the MI moment, since this hormone is an important hyperglycemic element and glucose regulator in ruminants. According to Horst & Jorgensen (1982) and Forslund *et al*. (2010) this hormone is considered an efficient indicator of stress and its elevation has been demonstrated in cows with parturient paresis and hypocalcemia. The recovery of the clinical condition of these animals was reflected in the endocrine regulation, with a reduction in the values of these variables (insulin and cortisol) observed at the MF moment.

5. Conclusions

The magnitude of alterations in blood metabolites reflected in NEB, in liver injury and stress level, portrays the negative impact that caused by digestive disorders of a fermentative nature, triggered in the dairy cows studied, especially ruminal acidosis, abomasal displacement, and cecal dilation.

The understanding of the dynamics of the biochemical metabolites analyzed is fundamental because it represents a key element in the diagnosis and in the evaluation of the response to the therapy used, but mainly because it contributes to greater precision in the prognosis.

The search for biochemical indicators in veterinary medicine, particularly in cattle breeding, envisages the possibility of avoiding greater economic losses, as well as improving animal welfare, constituting tools applied in the maintenance of the health of the herds.

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