SCIENTIFIC HORIZONS

Journal homepage: https://sciencehorizon.com.ua
Scientific Horizons, 26(5), 9-20

UDC 619:616-008.9:619
DOI: 10.48077/scihor5.2023.09

Prevention of subclinical ketosis in cows during drying off and after calving

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Article's History:
Received: 1.03.2023
Revised: 15.04.2023
Accepted: 2.05.2023

Suggested Citation:
Shkromada, O., Vlasenko, Ye., Panasenko, O., Baydevliatov, Yu., & Fotin, A. (2023). Prevention of subclinical ketosis in cows during drying off and after calving. *Scientific Horizons*, 26(5), 9-20.

Abstract. Research of the frequency of increased ketone bodies in cows during the transition period three weeks before calving and three weeks after calving should determine the tendency of the Holstein breed to ketosis. It is also important to investigate the relationship between changes in blood biochemical parameters and the development and treatment of ketosis. The purpose of the study was to determine the effectiveness of using a probiotic strain of bacteria in subclinical ketosis in cows during drying off and after calving. The following methods were used: testing for determining the level of beta-ketones in the blood of cows; biochemical method of blood testing; clinical method; statistical method. A study of cows in the drying off group showed that the level of β-ketones ranged from 0.2 to 1.0 mmol/L. Application efficiency of *Bacillus Pumilus* L. A 56 in a concentration of 1×10^9, CFU/g at a dose of 30 g per animal was determined

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to be 100%. In the study of metabolic changes in the body of cows after calving patients with ketosis, the content of total protein, albumins globulins of the enzyme aspartate aminotransferase, and urea at the beginning of the study was increased and went beyond the maximum permissible limits of the reference level. After seven days of using the probiotic, the content of ketone bodies and biochemical parameters decreased to normal. It was proved that at the end of the study, the activity of alanine aminotransferase increased, the level of potassium, vitamins A and E increased. Thus, it was determined that the enzyme alanine aminotransferase is one of the metabolites, an increase in the level of which indicates the accumulation of lipids in the liver. In addition, the content of Ca, P, and vitamin D decreased during treatment, which indicates the risk of hypocationemia. In the group of cows after calving, the incidence of ketosis was 27%. The therapeutic efficacy of a probiotic of 35 g per animal in the post-calving distribution group was 73%. The practical value of the study lies in the prevention of subclinical ketosis in cows in deep drying off and after calving, reducing the cost of treating concomitant diseases, and culling animals.

Keywords: ketone bodies; probiotic; metabolic disorders; negative energy balance; enzyme activity; vitamin and mineral balance

INTRODUCTION

The period in cows three weeks before calving (late drying off) and three weeks after calving is a stressful period due to metabolic disorders such as ketosis. Ketosis is a common metabolic disease that causes substantial economic losses for dairy farms. Despite the fact that selective selection for ketosis resistance has been examined by a large number of researchers (Yan *et al.,* 2020), the genetic and biological causes of ketosis are poorly understood.

Negative energy balance is one of the causes of ketosis in the postpartum period and can cause metabolic and immunological changes in cows. The stability of the immune defence is of great importance for protecting the animal from infectious diseases (Dai *et al.,* 2023). However, there are currently no studies on how negative balance affects the resistance of the body. Milk production technology determines the profitability of production. Diseases in cows cause an increase in the cost of veterinary care. Cows after calving often face diseases such as: ketosis, fatty hepatosis, cicatricial acidosis, mastitis, subclinical hypocalcemia, placental delay, and metritis.

Negative energy balance leads to increased formation of ketones as a result of the mobilisation of a large amount of lipids in the body. Metabolic disorders lead to a decrease in fertilisation and lactation. Researchers (Zhang *et al.,* 2020) prove that propylene glycol reduces the negative energy balance through gluconeogenesis and inhibits the synthesis of ketone bodies. However, a large dose of the drug (more than 500 g/day) has toxic effects and side effects in cows. Thus, there is a need for further studies of cow metabolism after calving.

All dairy cows have a negative energy balance because, at the beginning of distribution, the need for energy for milk production is greater than is obtained with feed (Dehghan Shahreza *et al.,* 2022). Negative energy balance is not always the cause of ketosis, and the main problem is how the cow overcomes metabolic adaptation during the transition period from pregnancy to calving. However, the researchers do not offer how to help the cow during the adaptation period and restore normal metabolism.

Researchers (Pascottini *et al.,* 2020) considered possible risk factors for cows in the prenatal period. It was determined that it is important to monitor adaptive changes in cows during drying off and after calving. However, studies have not considered the predisposition of certain breeds of cattle to metabolic diseases.

In addition, one of the most common diseases of the transition period, along with metabolic disorders of dairy cows, is mastitis, which has a clinical or subclinical manifestation (Zazharska *et al.,* 2021). Subclinical mastitis can only be diagnosed by determining indicators of inflammation or mastitis pathogens in milk (Fotina *et al.,* 2018). However, there is currently insufficient information on the relationship between the development of subclinical ketosis and udder inflammation in dairy cows during drying off and after calving.

A study by researchers (Mohsin *et al.,* 2022) proves that high levels of growth hormone in the postpartum period in the blood of cows with subclinical ketosis cause lipid mobilisation, which leads to hyperketonemia. There is a decrease in the level of amino acids and glycogen, and vice versa, an excess of ketogenic and lipogenic compounds (Nazeer *et al.,* 2019; Yang *et al.,* 2022). However, these studies lack information on the mechanism of the development of postpartum metabolic disorders in dairy cows.

In a study by (Delić *et al.,* 2020), differences in metabolism in the first week after calving between healthy cows and those with ketosis were determined. It was established that metabolic shifts can be predicted by the level of ketone bodies in the first week after calving. In sick cows, the level of beta-ketones was substantially higher (10.9-18.5%) than in healthy cows (2.5-9.1%). In addition, cows with ketosis tended to have elevated levels of total bilirubin and AST. The study allowed diagnosing ketosis early in cows after calving, but no possible way to prevent the disease has been proposed.

Genetic studies, conducted by (Weigel *et al.,* 2017) showed a tendency of Holstein cows to develop ketosis, especially in the postpartum period. The researchers do not offer possible solutions to this problem in their paper. It is also known (Cao *et al.,* 2017), that cows with clinical ketosis have high hematocrit and haemoglobin values, while the number of white blood cells (neutrophils and eosinophils) was substantially lower than in healthy ones. In addition, cows with ketosis show an increase in the level of unesterified fatty acids in the blood. However, there are no studies on the association of ketosis during deep drying off and the postpartum period with the biochemical parameters of blood serum.

The purpose of the study was to investigate the effect of probiotics on cows of the drying off period and after calving for subclinical mastitis. The objectives of the study were: investigation of the development of ketosis in cows during the period of deep drying off and after calving, determination of metabolic shifts in the body of dairy cows using a probiotic.

MATERIALS AND METHODS

The studies were conducted in the period from October to November 2021 on Holstein cows in the Limited Liability Company of the agricultural firm "Lan" of the North-Eastern region of Ukraine. A total of 81 animals were involved in the study, of which 27 were heads of deep drying off period and 54 – after calving.

The effectiveness of the probiotic was tested based on an experimental sample of the *Bacillus Pumilus* L. A 56 strain in a concentration of 1×10^9, CFU/g produced by the private enterprise "Kronos Agro" company. The dosage of the probiotic for the group after calving was 35 g per animal, in the group of deep drying off – 30 g. The animals received a diet according to the production group (Table 1-3).

Table 1. *Ration for cows, depending on the production group*

Ration	Milking 7 days after calving	Milking 14 days after calving	late drying off
Number of heads	133	152	42
silo	28	28	22
haylage	12	12	-
hay	3	3	1.5
straw	-	-	1.5
canned corn	6.5	6.5	2
mixed feed No. 2	8.5	8.5	-
Mixed feed No. 4	-	-	3.5

Table 2. *Mixed feed recipe No. 2 for cows (group after calving)*

No.	Component	% of input	per 500 kg	per 1 tonne, kg	for 1.5 tonnes, kg	for 2 tonnes, kg
1	Barley+Wheat	89	445	890	1335	1780
2	Premix TC VMP CD	7	35	70	105	140
3	Probiotic	3	15	30	45	60
4	Insorb	1	5	10	15	20
	Total	100	500	1000	1500	2000

Table 3. *Mixed feed recipe No. 4 for cows (late drying off)*

No.	Component	% of input	per 500 kg	per 1 tonne, kg	for 1.5 tonnes, kg	for 2 tonnes, kg
1	Barley+Wheat	26	130	260	390	520
2	Sunflower meal	67	335	670	1005	1340
3	Insorb	1	5	10	15	20
4	Prorbiotic	1	5	10	15	20
5	Premix TC VMP CS	5	25	50	75	100
	Total	100	500	1000	1500	2000

Note: *Premix TK ВМП КС of Tekro (Czech Republic), which includes a set of vitamins and microelements, according to the production group (drying off or milking cows)*
Source: *compiled by the authors*

Examination of cows for ketosis. The level of beta-ketones in the blood of cows was determined using a KetoSens ketometer (FDA). Blood for the examination was taken in the morning before feeding. Indicators were determined in cows of deep drying off (three weeks before calving) at the beginning of probiotic use and after seven days. The level of ketone bodies in cows was also determined on the seventh and fourteenth days after calving. The level of beta-ketones was used to determine sick cows that received additional treatment.

Examination of biochemical parameters of cow blood serum. Metabolic parameters were determined in seven cows from the post-calving distribution group with elevated levels of ketone bodies at the beginning and end of the study. The content of total protein (SOP-BP-02-2017), urea (SOP-BP-03-2017), albumin (SOP-BP-25-2018), urea nitrogen, Ca/P and globulins was determined by calculation, total cholesterol (SOP-BP-07-2017), aspartate aminotransferase AST (SOP-BP-09-2017), alanine aminotransferase ALT (sop-BP-08-2017), Total Ca (SOP-BP-05-2017), inorganic P (SOP-BP-04-2017), magnesium (SOP-BP-06-2017), potassium (SOP-BP-11-2017), vitamin E (SOP-BP-12-2018), vitamin A (SOP-BP-14-2018), vitamin D (25OH) (SOP-BP-18-2020).

Statistical analysis. Statistical data were calculated using the Fischer-Student method, considering statistical errors and the probability of comparable similar indicators. Indicators were considered probable with a level of more than 95% ($p<0.05$).

All experimental studies were conducted in accordance with modern methodological approaches and in compliance with the relevant requirements and standards, in particular, they comply with the requirements of DSTU ISO/IEC 17025:2005 (2006), in accordance with directive 2010/63/EU (Hartung, 2010), which were approved by the conclusion of the commission on ethics and bioethics of the Faculty of Veterinary Medicine of Sumy National Agrarian University dated 05.03.2022. The keep of animals and all manipulations were conducted in accordance with the provisions of the procedure for conducting experiments and experiments on animals by scientific institutions (Law of Ukraine No. 249, 2012), the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (European convention..., 1986).

RESULTS AND DISCUSSION

Results of the examination of cows for ketosis. The study began with the determination of the level of ketone bodies in animals during drying off and after calving (Table 4). During the experiment in all animals in the group of deep drying off (three weeks before calving) with the use of premix based on *Bacillus Pumilus* L. A 56 on the corresponding diet, the indicators fluctuated within the normal range from 0.2 to 1.0 mmol/L.

Table 4. *The level of ketone bodies in the blood of cows when using probiotic premix*

Late drying off group			Post-calving group					
No. of the animal	Start of the study	After 7 days	No. of the animal	7 days after calving	14 days after calving	No. of the animal	7 days after calving	14 days after calving
7658	1.0	0.8	7351	0.7	0	107	1.0	0
6266	1.0	0.8	6852	3.5	0.7	2522	0.9	0
6915	0.7	0.7	7658	0.7	0	3861	0.7	0
0357	0.7	0.5	1627	0.8	0	9683	0.7	0
0944	1.0	0.4	0340	1.1	1.0	6707	0.8	0
6949	0.8	0.8	6905	1.5	1.0	6896	0.5	0
7632	1.0	0.9	6266	1.1	0.8	2514	0.7	0
3061	0.7	0.6	3940	1.4	0.9	0982	0.4	0
1941	0.7	0.7	0944	0.8	0	6949	1.6	0.6
7603	0.7	0.8	6886	0.6	0	3928	0.5	0
7791	0.7	0.5	4089	0.7	0	6187	3.8	2.4
6281	0.7	0.6	6915	2.3	0.7	7633	0.7	0
6674	0.6	0.4	7497	0.6	0	2563	1.8	0.6
6870	0.6	0.7	4077	0.4	0	0357	0.7	0
1981	0.6	0.6	2545	1.3	0.7	7603	1.2	0.4
3929	0.5	0.6	3630	0.8	0	4636	0.6	0
7327	0.6	0.4	3061	1.4	0.5	7328	0.6	0
4584	0.2	0.2	19706	0.7	0	6657	1.0	0

Table 4, Continued

Late drying off group			Post-calving group					
No. of the animal	**Start of the study**	**After 7 days**	**No. of the animal**	**7 days after calving**	**14 days after calving**	**No. of the animal**	**7 days after calving**	**14 days after calving**
1008	0.7	0.7	1941	0.5	0	3853	0.7	0
6661	0.8	0.7	3086	0.6	0	7614	0.8	0
6843	0.7	0.6	6302	0.6	0	5892	0.6	0
6872	0.8	0.8	0314	0.8	0	7642	1.9	0.8
4325	1.0	0.5	7781	0.5	0	7696	0.5	0
3956	0.9	0.4	6133	0.5	0	7331	0.4	0
4853	0.7	0.6	3870	0.5	0	6674	0.3	0
1983	0.8	0.6	7640	0.8	0	9765	0.9	0
3942	0.7	0.5	3891	2.0	0.9	7791	0.4	0
Average value	0.73 ±0.03	0.60 ±0.03	Average value	-	-	-	1.79 ±0.19*	1.33 ±0.20*

Note: ** – p≤0.05, compared with similar indicators of the late drying off group with the post-calving distribution group*
Source*: compiled by the authors*

During the experiment, it was determined that in experimental animals of the late drying off group of 27 heads, the level of ketone bodies was lower than at the beginning of the study (1.0-0.2 mmol/L), and after seven days of using premix (0.9-0.2 mmol/L). There was no substantial difference in group scores at the beginning and end of the study, but the group average improved by 17.80%. The effectiveness of premix in the drying off group is 100%, no cases of increased ketone bodies were determined out of the 27 heads tested

In the milking group of 54 heads, seven days after calving, the level of ketone bodies in the blood of cows ranged from 3.5 to 0.3 mmol/L. On the 14th day after calving, the indicators ranged from 2.4 to 0 mmol/L. The difference between the initial and final values was 25.6%. In addition, out of 54 heads of the distribution group, 15 heads showed signs of clinical ketosis.

Thus, cow No. 6852 on the seventh day after calving had an 80% lower content of ketone bodies compared to the end of the study on Day 14. During the entire experiment, the level of beta-ketones decreased in animals No. 0340 by 9.09%, No. 6905 – by 33.33%, No. 6266 – by 27.27%, No. 3940 – by 35.71%, No. 6915 – by 69.56%, No. 2545 – by 46.15%, No. 3061 – by 64.28%, No. 3891 – by 55.00%, No. 107 – by 100%, No. 6949 – by 62.50%, No. 2563, and No. 7603 – by 66.66%, No. 7642 – by 57.89%, compared to the beginning of the study.

Additionally, 15 heads were treated, 14 heads were cured, and 1 head had a relapse of the disease. It should also be noted that there was a substantial difference between similar indicators of the beginning and end of the experiment in the groups of deep drying off and milking after calving. All animals in which the indicators of ketone bodies were increased were prescribed specific treatment with drugs based on hepatoprotectors and minerals, animals are better able to recover, they have a reduced indicator of ketone bodies, relapses decreased to a minimum, and all animals in which ketone bodies were increased retained milk productivity, after completing treatment gained total weight faster. The overall incidence rate is 27% out of 100%, and the effectiveness of treatment is 73%.

Results of the study of biochemical parameters of cow blood serum. For the effect of premix on the animal body, blood tests were performed at the beginning and after performing the experiment in a group of animals after calving (Table 5-7).

Table 5. *Results of biochemical studies of cow blood serum, M±m, n=3*

No.	Start of the study	Indicators							
	End of the study	**Total protein, g/L**	**Albumins, g/L**	**Globulins, g/L**	**Albumins, %**	**Globulins, %**	**(A/G), units**	**Urea, mmol/L**	**Urea nitrogen, mg/dL**
No. of the animal		**SOP-BP-02-2017**	**SOP-BP-25-2018**	**Calculation**				**SOP-BP-03-2017**	**Calculation**
1	6905	75.09 ±0.45	35.42 ±0.68*	40.67 ±0.33	46.45 ±0.62*	53.63 ±0.80*	0.84 ±0.04	8.26 ±0.50*	22.43 ±0.48*
		74.90 ±0.09	31.61 ±0.96	42.34 ±1.13	42.33 ±0.54	57.50 ±0.43	0.76 ±0.06	5.37 ±0.61	14.69 ±0.73

Table 5, Continued

No.	Start of the study / End of the study	Total protein, g/L	Albumins, g/L	Globulins, g/L	Albumins, %	Globulins, %	(A/G), units	Urea, mmol/L	Urea nitrogen, mg/dL
No. of the animal		SOP-BP-02-2017	SOP-BP-25-2018	Calculation				SOP-BP-03-2017	Calculation
2	6852	86.80 ±0.81*	31.40 ±0.58	55.20 ±0.50*	36.75 ±0.39	63.33 ±0.37*	0.58 ±0.01*	6.35 ±0.04*	17.72 ±0.15
		73.54 ±0.76	33.35 2.3.	40.66 ±0.85	45.24 ±0.43*	54.81 ±0.51	0.82 ±0.01	6.96 ±0.07	19.48 ±0.29
3	6915	79.48 ±0.30*	33.55 ±0.28	45.62 ±0.34	42.37 ±0.31	57.53 ±0.39	0.73 ±0.04	8.43 ±0.28	23.45 ±0.37
		72.88 ±0.36	32.59 ±0.37	40.60 ±0.85	43.62 ±0.57	56.03 ±0.67	0.76 ±0.06	8.21 ±0.14	23.26 ±0.39
4	7642	81.35 ±0.33*	31.18 ±0.41*	50.42 ±0.46*	38.26 ±0.40*	61.67 ±0.69*	0.63 ±0.05*	5.87 ±0.33	16.57 ±0.43
		89.19 2.3.	23.92 ±0.19	65.17 ±0.62	26, 80 ±0.75	73.11 ±0.56	0.37 ±0.02	6.31 ±0.53	17.31 ±0.50
5	6187	72.24 ±0.61*	36.42 ±0.54	35.63 ±0.83*	50.20 ±0.65*	49.84 ±0.77*	1.01 ±0.01	7.98 ±0.30*	22.18 ±0.42*
		75.63 ±0.37	32.33 ±0.48	43.31 ±0.46	42.67 ±0.71	57.36 ±0.53	0.73 ±0.04	6.18 ±0.44	17.26 ±0.49
6	2563	68.39 ±0.40*	30.70 ±0.71*	37.73 ±0.68*	44.88 ±0.18*	55.42 ±0.47*	0.83 ±0.05*	6.83 ±0.18	19.11 ±0.68
		95.70 ±0.18	24.77 ±0.72	71.08 ±0.48	25.63 ±0.41	74.22 ±0.43	0.35 ±0.04	6.53 ±0.40	18.13 ±0.93
7	3891	63.39 ±0.56*	31.81 ±0.21	31.77 ±0.53*	49.57 ±0.41*	50.26 ±0.80*	0.95 ±0.15	5.14 ±0.40	14.51 ±0.47*
		87.08 ±0.69	31.12 ±0.39	55.79 ±0.29	35.64 ±0.58	64.42 ±0.54	0.56 ±0.12	4.32 ±0.39	11.49 ±0.32
Reference values		59-85	27-43	25-45	38-50	50-62	0.6-1.1	3.30-6.70	8-20

Note: ** – p⩽0.05, compared to the start of the study*
Source: *compiled by the authors*

It was determined that the albumin level of cow No. 6905 was substantially higher by 10.7%, compared to the beginning and end of studies, but within the physiological norm. The content of urea and urea nitrogen was increased by 34.98% and exceeded the reference level. At the start of the study, the AST enzyme was substantially higher by 24.18% compared to the end of treatment.

Vitamin and mineral metabolism in animal No. 6905 was within the physiological norm, and the vitamin A content increased by 6.81% at the end of the study. In cow No. 6852, the level of total protein, globulins, and albumins was higher than the permissible limits of the reference level at the beginning of treatment. At the end of the study, all indicators returned to normal. Initial examination in cow No. 6852 showed substantially higher total protein content by 11.04%, globulins – by 8.52%, and albumins – by 14.54%. Urea and urea nitrogen levels were higher by 9.60-9.93%, respectively.

The level of the AST enzyme was higher than the reference level at the start of the study. At the end of the experiment, the level of AST substantially decreased by 12.95%. However, ALT levels at the beginning of treatment were 50.34% lower compared to data after seven days. The content of calcium and phosphorus in the animal's blood serum was within the physiological norm and practically did not differ during the entire study period. The level of potassium in the blood of cow No. 6852 at the end of the study increased by 30.52% and went beyond the upper limit of the reference level. In addition, the content of vitamin E increased by 56.30%, vitamin A – by 10.42% and vitamin D – by 29.27%. It should be indicated that the level of magnesium in the blood serum of animals with ketosis was within the physiological norm.

Table 6. *Biochemical examination of cow blood serum, M±m, n=3*

No.	Start of the study / End of the study	Indicators						
		Total cholesterol, mmol/L	AST, units/L	ALT, units/L	(AST/Alt), units	Total Ca, mmol/L	Inorganic P, mmol/L	Ca/P, units
No. of the animal		SOP-BP-07-2017	SOP-BP-09-2017	SOP-BP-08-2017	Calculation	SOP-BP-05-2017	SOP-BP-04-2017	Calculation
1	6905	5.81 ±0.47	106.45 ±3.07*	30.85 ±1.05	2.74 ±0.25	2.20±0.16	2.27±0.41	1.19±0.13
		3.51 ±0.48	80.70 ±0.84	31.687 ±0.49	3.41 ±0.35	1.98±0.26	1.79±0.13	1.11±0.06
2	6852	3.08 ±0.52	113.22 ±1.52*	18.97 ±1.19*	6.14 ±0.77*	2.93±0.14	1.93±0.18	1.54±0.40
		4.44 ±0.41	98.55 ±3.33	28.52 ±1.00	3.38 ±0.54	2.19±0.32	2.01±0.12	1.08±0.04
3	6915	4.13 ±0.47	108.47 ±4.84	24.68 ±0.54*	4.42 ±0.58	2.84±0.09	2.04±0.26	1.36±0.36
		3.10 ±0.35	101.18 ±1.17	27.16 ±0.45	3.70 ±0.22	2.13±0.30	1.88±0.20	1.18±0.37
4	7642	2.76 ±0.52	91.64 ±3.84	25.50 ±0.46*	3.65 ±0.25	2.48±0.26	2.30±0.28	1.08±0.05
		2.12 ±0.48	85.51 ±1.00	17.86 ±0.77	4.54 ±0.72	1.68±0.31	2.20±0.29	0.74±0.03
5	6187	5.62 ±0.92	147.4 ±2.46*	33.37 ±0.45	4.33 ±0.51*	2.42±0.28	2.06±0.37	1.16±0.34
		5.02 ±0.58	67.32 ±0.51	32.52 ±0.57	2.09 ±0.21	2.11±0.55	2.04±0.38	1.07±0.05
6	2563	2.09 ±0.54	113.26 ±1.55*	15.33 ±0.42	7.36 ±0.75*	1.85±0.28	2.04±0.18	0.95±0.10
		2.31 ±0.47	78.96 ±0.88	16.28 ±1.03	4.72 ±0.45	2.06±0.51	2.02±0.17	1.07±0.17
7	3891	1.88 ±0.46*	90.70 ±1.44*	17.54 ±0.40*	5.14 ±0.55	2.03±0.48	2.37±0.34	0.88±0.16
		4.39 ±0.58	79.81 ±0.7	20.81 ± 0.58	3.83 ±0.66	2.13±0.67	2.12±0.19	1.04±0.04
Reference values		2.20-6.60	2.20-6.60	48-108	17-40	1.0-3.4	1.98-3.12	1.50-2.90

Note: ** – p⩽0.05, compared to the start of the study*
Source: *compiled by the authors*

On the seventh day after calving, cow No. 6915 had an increased level of total protein by 8.30%, assumably due to an imbalance towards globulins by 15.16%, compared to albumin. After seven days of using a probiotic strain-based premix *Bacillus Pumilus* L. A 56 globulin levels decreased by 11.00%. The urea level was high and exceeded the upper limit of the physiological norm. At the end of the experiment, the content of urea and urea nitrogen decreased by 2.60% and 0.82%, respectively, but the indicators still exceeded the reference limits. The level of AST in the blood serum of cow No. 6915 at the beginning of the study was higher by 10.63%. After seven days, ALT, on the contrary, increased by 10.04%. Therewith, the AST/ALT ratio was higher by 16.28% and went beyond the reference level. Calcium and phosphorus levels were within normal limits throughout the study period. In addition, on the 14th day of the study, the level of potassium increased by 33.74%, vitamin E – by 55.18%, vitamin A – by 8.46, and vitamin D – by 15.18%, but all within the physiological norm.

Notably, in the conducted studies, the content of total cholesterol in the blood serum of cows with ketosis during the entire treatment period fluctuated in cows No. 6905, No. 6852, and No. 6915 and did not exceed the reference level. The exception was animals No. 2563 and No. 3891, whose cholesterol levels were lower by

10.52% and 133.51%, respectively, at the beginning of the study, which indicates a recovery in liver function. In addition, the cholesterol level of animal No. 7642 decreased by 23.18% at the end of the study. Therewith, the level of AST in animal No. 7642 decreased at the end of the study by 6.68%, AlLT – by 29.96%, total Ca – by 3.25%, inorganic P – by 4.34%. In addition, in cow No. 7642, the total protein content decreased by 9.63%, albumin – by 23.28%, globulin increased by 29.25%, compared to the beginning of the study. The globulin content exceeded the upper permissible limit of the reference level at the beginning and end of the study. In addition, the animal's potassium and magnesium content did not change during the studies, vitamin E increased by 25.53%, vitamin A – by 4.94%, and vitamin D decreased by 44.09% (below the reference level), compared to the beginning. The results indicate severe metabolic adaptation in cow No. 7642 during the transition period.

In animal No. 6187, the level of total protein increased by 4.69%, globulins – by 21.55%, albumins decreased by 11.23%, urea content increased by 22.55% and urea nitrogen – by 22.18%, compared to the beginning of studies and above the reference level.

Table 7. *Vitamin and mineral composition of cow blood*

No.	Start of the study / End of the study	Indicators				
		Magnesium, mmol/L	Potassium, mmol/L	Vitamin E, mcg/ml	Vitamin A, mcg%	Vitamin D (25OH), ng/ml
No. of the animal		SOP-BP-06-2017	SOP-BP-11-2017	SOP-BP-12-2018	SOP-BP-14-2018	SOP-BP-18-2020
1	6905	1.02±0.05	4.15±0.58	3.19±0.51	44.48±0.82*	22.07±0.38
		1.03±0.04	4.56±0.36	4.30±0.74	47.52±0.55	22.54±0.56
2	6852	1.11±0.08	4.39±0.37	3.41±0.35	45.10±0.63*	32.55±0.61*
		0.88±0.23	5.73±0.72	5.33±0.74	49.80±0.95	23.02±0.64
3	6915	1.01±0.09	4.15±0.14	3.43±0.35	44.43±0.45*	36.16±0.53*
		0.95±0.15	5.55±0.70	5.27±0.78	48.19±0.52	41.65±0.42
4	7642	1.08±0.20	5.03±0.87	3.87±0.84	44.25±0.34	22.52±0.64
		1.06±0.07	5.18±0.79	4.86±0.41	46.44±0.73	12.59±0.36
5	6187	0.97±0.12	4.92±0.53	3.62±0.24	44.93±0.63*	20.06±0.55
		0.90±0.14	5.60±0.70	4.72±0.57	47.94±0.54	22.35±0.66
6	2563	1.10±0.31	3.73±0.32	3.16±0.24	43.76±0.94*	43.0±0.89*
		0.79±0.07	5.62±0.71	4.90±0.65	49.19±0.63	24.94±0.51
7	3891	1.01±0.23	4.07±0.55	3.00±0.33	46.19±0.67	55.06±0.60*
		0.95±0.14	6.40±1.02	5.20±0.82	48.16±0.58	16.67±0.74
Reference values		0.70-1.23	0.70-1.23	4.0-5.3	2.0-9.0	25.0-80.0

Note: ** – p≤0.05, compared to the start of the study*
Source*: compiled by the authors*

The level of total protein in animal No. 2563 increased by 39.93%, assumably due to globulins – by 88.39%, while the content of albumins decreased – by 19.31%. The content of urea and urea nitrogen decreased by 4.39% and 10.71%, respectively. The indicators went beyond the reference level.

At the end of the experiment, the level of the AST enzyme decreased by 30.28%, and ALT increased by 6.19%. At the beginning of the study, AST and ALT levels exceeded the physiological norm. The total Ca content was 11.35% lower than standard indicators at the start of the study compared to the end of treatment. Also in cow No. 2563, the level of potassium increased by 50.67%, vitamin E – by 55.06%, vitamin A – by 12.40%, and vitamin D decreased by 42.00%.

At the end of the study, the total protein content in cow No. 3891 increased by 37.37%, globulins – by 75.60% and went beyond the reference level. Urea levels substantially decreased by 15.95% and urea nitrogen – by 20.81%, compared to the beginning of the study. The level of the AST enzyme decreased by 12.0%, alt increased by 18.64%, Ca/P ratio – by 18.18%, compared to the beginning of the study. The content of potassium substantially increased by 57.27%, vitamin E – by 73.33%, vitamin A – by 4.26%, vitamin D decreased – by 30.23%.

According to the results of the conducted studies on cows with ketosis, the positive effect of using a probiotic based on *Bacillus Pumilus* L. A 56 in a concentration of 1×10^9, CFU/g in the dry period of 30 g per animal, and 35 g per animal after calving, was proved.

The study showed that all animals in the deep drying off group had a ketone body level of no more than 1.0 mmol/L (Zhang *et al.,* 2021). Researchers (Daros *et al.,* 2020) believe that limping cows in deep drying off are at risk of developing diseases such as ketosis, metritis, placental retention, hypocalcemia, and rennet displacement. Therefore, much attention is paid to all pregnant animals on the farm, especially during the transition dry and postpartum period.

A week after calving, the ketone body levels of 54 animals increased. Seven days after applying a probiotic based on *Bacillus Pumilus* L. A 56, indicators decreased to normal, except for 15 heads. Researchers (Rodriguez *et al.,* 2022) in their studies report that ketosis in the first week of lactation in cows is due to low milk yields. In the second week of lactation, this trend was not recorded. However, the model developed by researchers is not perfect, has assumptions and is limited by current research.

Researchers (Ayemele *et al.,* 2021) determined that the introduction of amino acids, vitamins, microelements, and plant extracts into the diet of cows exposed to oxidative stress showed promising results due to the strengthening of immune functions and the repair of damaged cells.

Studies by (Denis-Robichaud *et al.,* 2022; Williamson *et al.,* 2022) confirm that the ketone body levels in the range of 1.2 to 2.9 mmol/L are a signal of possible exacerbation of ketosis and health risks during early lactation. The critical point for the occurrence of subclinical ketosis is the level of ketone bodies in the blood greater than 1.2 mmol/l, and a critical level – greater than 3.0 mmol/L usually indicates the development of a clinical form.

ALT levels have increased by the end of the study. This proves that ALT levels are associated with manifestations of ketosis in cows and can fluctuate during treatment (Pinedo *et al*., 2021).

Researchers (Gross & Bruckmaier, 2019) determined that low albumin levels usually indicate liver failure. Previous studies by researchers (Kozat & Yüksek, 2017) showed that ALT is insensitive to ketosis in cows. However, in other studies (Du *et al*., 2017), liver apoptosis and high ALT levels were observed in dairy cows with ketosis.

When investigating the biochemical parameters of blood serum in cows with signs of ketosis, it was determined that in animals the content of total protein, globulins, and albumins fluctuated within the maximum permissible limits and even went beyond them (Ha *et al.,* 2022). In addition, (Puppel *et al.,* 2019) observed increased urea and urea nitrogen content, which decreased at the end of treatment. The aspartate aminotransferase (AST) enzyme is an indicator of liver and muscle function (Ma *et al.,* 2022). An increase in AST at the beginning of treatment indicates a substantial load on the liver, while ALT increased at the end of the study (Theinert *et al.,* 2022). A study by researchers (Giannuzzi *et al.,* 2021) determined that cows with ketosis have increased levels of aspartate aminotransferase and cholesterol.

The group of animals with ketosis included cows with a body condition of more than three points, who also had complications such as placental delay and metritis. Studies (Garzón-Audor & Oliver-Espinosa, 2019) have shown that the overall frequency of ketosis in dairy cows is 26% of all animals examined.

Ca and P levels were determined to be associated with ketosis and depend on the manifestation of the disease (Pacífico *et al*., 2021). Blood magnesium levels did not change substantially throughout the experiment. The content of potassium, vitamins A and E increased at the end of treatment. Therewith, the vitamin D content decreased in all experimental cows, regardless of the severity of the metabolic adaptation of the body. It is believed that a substantial amount of vitamins and minerals was involved in the restoration of metabolism in the body of animals, and therefore their level in the blood serum was not high.

CONCLUSIONS

It was determined that in cows in the group of deep drying off on the corresponding diet, the content of ketone bodies ranged from 0.2 to 1.0 mmol/L. After using the probiotic, the average number of ketone bodies in the group improved by 17.80%. The effectiveness of using premix in the drying off group was 100%.

In the distribution group, seven days after calving, the level of ketone bodies in the blood of cows ranged from 0.3 to 3.5 mmol/L, the incidence rate was 27%. Two weeks after the probiotic was administered, the ketone level was in the range of 2.4 to 0 mmol/L, which is a 25.6% decrease compared to the start of the study.

The overall incidence rate in the post-calving distribution group was 27% out of 100%, and the therapeutic efficacy of probiotic use was 73%. 15 cows out of 54 needed additional treatment, 14 heads fully recovered, and one animal had a relapse of the disease.

Studies of metabolic shifts in the body of cows showed that the level of urea was high and went beyond the upper limit of the physiological norm. At the beginning of the study, cows had an increased total protein content of 8.30-11.04%, globulins – by 8.52-11.00%, albumins – by 10.7-14.54%. At the end of the experiment, the content of urea and urea nitrogen decreased by 2.60-0.82%. The level of AST in the blood serum of cows at the beginning of the study was higher by 6.68-10.63%. After seven days of probiotic use, ALT increased by 10.04-29.96%. Ca, P, and vitamin D levels

decreased during treatment, but potassium, vitamins A, and E levels recovered. The prospect of further research is to determine the dependence of the occurrence of ketosis in dairy cows depending on the size of the fetus and the number of lactations.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

None.

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Профілактика субклінічного кетозу у корів сухостійного періоду та після отелення

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Анотація. Дослідження частоти підвищення кетонових тіл у корів у перехідний період за три тижні до родів та три тижні після отелення має визначити схильність голштинської породи до кетозу. Також важливо дослідити взаємозв'язок у зміні біохімічних показників крові, розвитку і лікуванню кетозу. Метою дослідження було визначити ефективність застосування пробіотичного штаму бактерій за субклінічного кетозу у корів сухостійного періоду та після отелення. Використані методи: тест для визначення рівня β-кетонів в крові корів; біохімічний метод дослідження крові; клінічний метод; статистичний метод. Дослідження корів в групі сухостою показало, що рівень β-кетонів коливався в межах від 0,2 до 1,0 ммоль/л. Ефективність застосування *Bacillus Pumilus* L. A 56 в концентрації 1×10^9, КУО/г в дозі 30 г на тварину показало 100 %. При дослідженні метаболічних змін в організмі корів після отелення хворих на кетоз вміст загального білка, альбумінів глобулінів ферменту аспартатамінотрансферази та сечовини на початку дослідження був підвищений і виходив за межі максимально допустимих меж референтного рівня. Через сім діб застосування пробіотику вміст кетонових тіл та біохімічні показники знижувався до норми. Доведено, по завершенню дослідження збільшувалась активність аланінамінотрансферази, збільшився рівень Калію, вітамінів А та Е. Таким чином встановлено, що фермент аланінамінотрансфераза є одним з метаболітів, підвищенні рівня якого вказує на накопичення ліпідів в печінці. Крім того, вміст Са, Р та вітаміну D знизився протягом лікування, що вказує на загрозу виникнення гіпокаціємії. В групі корів роздій після отелення захворюваність на кетоз склала 27 %. Терапевтична ефективність від застосування пробіотику 35 г на тварину у групі роздій після отелення становила 73 %. Практична цінність дослідження полягає у профілактиці субклінічного кетозу у корів глибокого сухостою та після отелення, зменшення витрат лікування супутніх захворювань та вибракування тварин

Ключові слова: кетонові тіла; пробіотик; метаболічні розлади; негативний енергетичний баланс; активність ферментів; вітаміно-мінеральний баланс