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ORIGINAL ARTICLE

Functional state of the liver in cows with fatty liver disease

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Studies in dairy farms have shown that the leading causes of fatty liver disease were violations of the structure of rations, imbalance of feeding on the primary nutrients, and biologically active substances. The study was performed on cows aged 4–5 years with productivity for the previous lactation of 5,600–7,500 L of milk, in a winter-stall period of keeping, 2–3 weeks after calving. According to clinical and biochemical blood tests, two groups of cows were formed – 50 clinically healthy and 50 cows with fatty liver disease. Clinically, the disease was manifested in general and in some cows by typical symptoms. The blood serum of all cows with fatty liver disease established a decrease in albumin content, indicating impaired protein synthesis function of the liver. Dystrophic changes in hepatocytes, irritation of reticuloendothelial system cells by exotoxins and endotoxins, which accumulate during liver damage, cause the excessive formation of globulins, increased content of total serum protein, and the development of dysproteinemia. In the blood of all cows with the fatty liver disease increases the concentration of bile acids. The formation, absorption, conjugation, and excretion of bilirubin in the bile is disturbed, which causes the accumulation of total and conjugated bilirubin in the serum of cows. The cholesterol content in the blood of cows decreased, caused a violation of the esterification of its esters by hepatocytes. The established changes in the content of bile acids, total and conjugated bilirubin, and cholesterol in the blood of sick cows indicate a violation of bile secretion, bile production, and cholestasis development. In some cows with fatty liver disease, urea formation function and carbohydrate function are impaired, leading to a decrease in blood urea content and glucose.
Keywords: cows; fatty liver disease; symptoms; biochemical blood parameters; liver functions.

Introduction

The high milk productivity of cows on farms largely depends on their health. The average productive life expectancy of cows in countries with highly developed dairy farming is an average of 3–4 years (Klug et al., 2004; Gruber & Mansfeld, 2019; Grymak et al., 2020). This is much less than the natural lifespan of dairy cattle. Cow culling in farms is associated with decreased milk productivity and impaired reproductive function, which is a consequence of various pathologies' development (De Vries & Marcondes, 2020). The cause of morbidity in dairy farms is technological processes violation of keeping and feeding highly productive cows (Ingvartsen, 2006; Smith et al., 2017). The diseases are widespread in the postpartum period. After calving, dairy cows are often diagnosed with metabolic pathologies and lesions of the internal organs. In particular, liver diseases in cows occupies a leading place, and they are much more common than is considered because the pathology is subclinical or has general and nonspecific symptoms (Bobe et al., 2004; Levchenko et al., 2012; Roman et al., 2020; Slivinska et al., 2020; 2021). Highly productive cows often sick by fatty liver disease, which in the scientific literature is also called hepatic lipidosis (Dirksen et al., 2002; Kalaitzakis et al., 2010; Levchenko et al., 2012). The pathology causes disruption of essential functions and structure of the liver, as well as metabolism in the whole body, which leads to decrease of productivity, damage of other vital organs and systems, and premature culling of highly productive animals (West, 1989; González al., 2011).

In liver cells synthesized the main proteins of blood plasma, bilirubin, bile acids, cholesterol, essential processes of carbohydrate conversion take place, exo- and endotoxins are neutralized, urea is formed. The liver regulates the level of formed products and their release into the blood and bile. However, as the literature analysis shows, the state of basic liver functions in its damage often depends on the selection of dairy breeds, adaptation to new conditions of detention after import from abroad, feeding features (Grummer, 2007; Vlizlo et al., 2020). Therefore, it is crucial to analyze the functional state of the liver in cows in each farm where the disease is diagnosed.

The purpose of the work was to study the state of protein synthesis function, urea formation function, carbohydrate function, bile production, and secretion functions of the liver in cows with fatty liver disease.

Materials and Methods

The study was performed on cows aged 4–5 years with productivity for the previous lactation of 5600–7500 l of milk, in a winter-stall period of keeping, 2–3 weeks after calving. At the beginning of the experiment, according to the results of clinical and biochemical blood tests, two groups of cows were formed – 50 clinically healthy and 50 cows with fatty liver disease. During the clinical study, special attention was paid to the color of the sclera, visible mucous membranes, unpigmented areas of skin, and pain of the liver and its enlargement.

Blood for researches was obtained from the jugular vein in the morning before feeding. The protein synthesis function of the liver was determined by the content in the blood serum of total protein (biuret reaction) and protein fractions (polyacrylamide gel electrophoresis); carbohydrate function – by the content in the blood of glucose (enzymatic glucose-oxidase method); bile production and secretion functions – by the content in the blood serum of bile acids (enzymatic reaction with a test system of the company "SENTINEL"), total cholesterol (Ilko method), total and conjugated bilirubin (Jendrassik and Grof method in modification of Levchenko and Vlizlo); urea formation function – by the content in the blood serum of urea (reaction with diacetylmonoxime).

After the forced slaughter of cows, a veterinary and sanitary examination was performed, paying particular attention to the structure of the liver.

The research was performed following the rules for the performance of zootechnical experiments for the selection and keeping of animals-analogs in groups, the technology of harvesting, use, and accounting of consumed feed.

All manipulations with animals were carried out under the European Convention for the Protection of Vertebrate Animals, used for Experimental and Scientific Purposes (Official Journal of the European Union L276/33, 2010).

The mathematical processing of the research results was worked out statistically using a program package Statistica 6.0 software (Stat Soft, Tulsa, USA). Differences between the mean values were considered statistically significant at $P < 0.05$ (ANOVA, considering the Bonferroni Correction).

Results

The survey and analysis of farms where the research was conducted indicated violations of management on farms. In particular, year-round stall technology of keeping was used for cows without exercise and grazing. There was no maternity ward on the farms and separate rooms for dry cows and the main dairy herd.

In the diet structure of dry cows in the winter period of keeping the share of concentrated feed by metabolic energy was 11%, roughage – 11%, succulent – 78%. The energy intensity of the diet provided the needs of cows by 150.2% and was 174.2 MJ. The amount of digestible protein in the diet of dry cows provided their need by 106.4%, and sugar – by 73.3%. The sugar-protein ratio was 0.6 to 1.0, at norm 0.8–1.2 to 1.0. In addition, the diet of dry cows lacked crude fiber (provided by 77.6%). During the dry period, higher fatness and obesity were recorded in some cows.

In the diet of the postpartum period in dairy cows, the calculation of metabolic energy was dominated by succulent feed 75%, the share of roughage was 2%, and concentrated – 23%. The energy intensity of the diet was 125 MJ and provided the need by 90%. The dry matter content of the feed was higher by 21.3%. At the same time, providing cows by crude fiber was relatively low and amounted to 83.8%. The digestible protein content provided the body by 145.6%, the amount of sugar in the diet was low and amounted to 71% of need. The sugar-protein ratio was only 0.5 to 1.0, at norm 0.8–1.2, to 1.0.

Cows were sometimes fed large quantities of corn bard, which had a putrid odor on organoleptic examination and was brown. Veterinary sanitary examinations of cows that were forcibly slaughtered showed that most animals were diagnosed with fatty liver disease. The pathology was registered in the postpartum period.

In cows with fatty liver disease, decreased milk productivity and fatness (coefficient of fatness was from 1.5 to 3.0). The general condition was a depression in sick animals, found dryness and decreased skin elasticity, decreased appetite, hypotension of the rumen, reticulum, and omasum. Visible mucous membranes were pale pink, pink or pale. Jaundice of the visible mucous membranes and sclera was recorded in single cows. In some cows, there was a pain in the liver area and increasing boundaries of hepatic dullness. Fecal masses were dry, in some cows covered with mucus, sometimes diarrhea was observed. Some sick cows were simultaneously diagnosed with pododermatitis, mastitis, endometritis.

In the blood serum of cows with fatty liver disease, decreased albumin content. The decrease was significant both in absolute (Fig. 1) and in relative value (26.6 ± 0.31%, compared to 42.4 ± 0.30% in clinically healthy, $P<0.001$) from all fractions of total protein.

However, the content of serum total protein in sick cows increased to 87.5 ± 0.34 g/L ($P<0.001$) compared to 77.7 ± 0.40 g/L in clinically healthy. This was due to an increase ($P<0.001$) in the number of alpha-, beta- and gamma globulin fractions. The increase of globulins content and decrease of albumins in the blood serum of sick cows led to a decrease of albumin-globulin ratio to 0.4 ± 0.01 ($P<0.001$), compared to 0.74 ± 0.03 in clinically healthy, and the development of dysproteinemia.

The urea content in the serum of cows with fatty liver disease was 35% lower ($P<0.001$) compared to clinically healthy animals (Fig. 2).

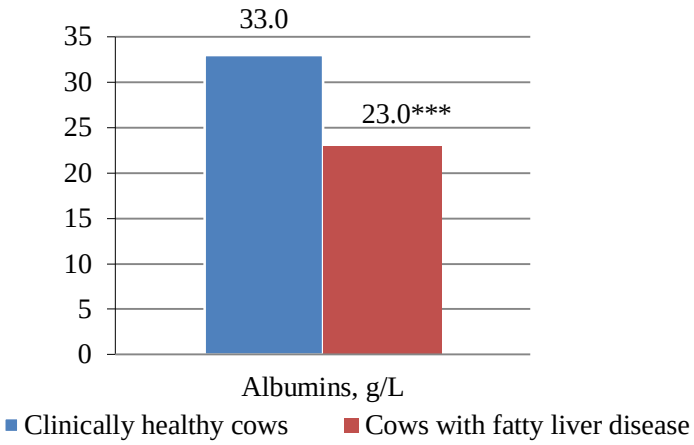

Fig. 1. The albumin content in the blood serum of cows

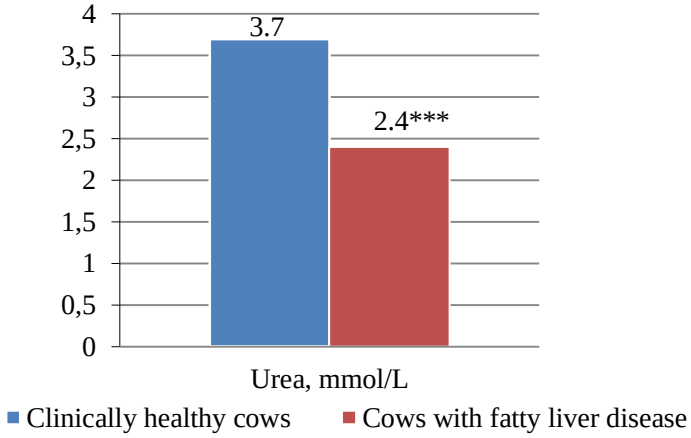

Fig. 2. The urea content in the blood serum of cows.

At the same time, the content of glucose in the blood of sick cows decreased by 1.6 times (P<0.001) compared to clinically healthy (Fig. 3).

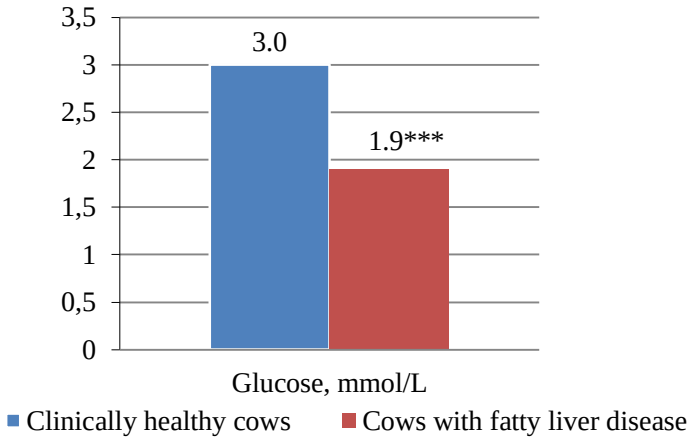

Fig. 3. The glucose content in the blood of cows.

In the serum of cows with fatty liver disease, the content of bile acids increased in all animals and was by 4.4 times higher (P<0.001) compared to clinically healthy animals (Fig. 4).

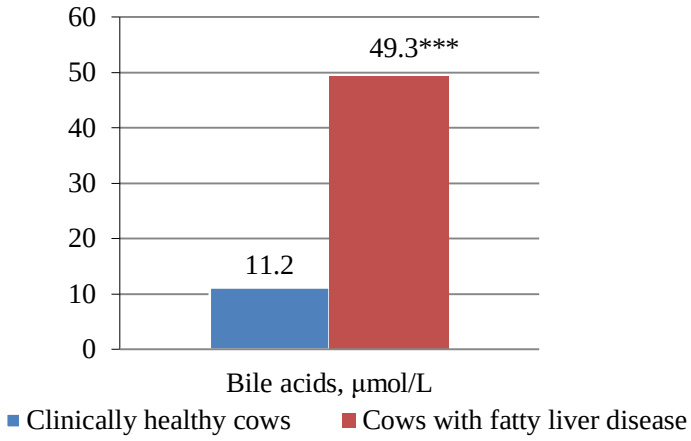

Fig. 4. The bile acids content in the blood serum of cows

Similar changes were established during the determination of serum bilirubin (Fig. 5). Thus, the total bilirubin content in the blood serum of cows with the fatty liver disease increased by 4.2 times ($p<0.001$), and conjugated bilirubin – by 2.9 times ($P<0.001$), compared to clinically healthy.

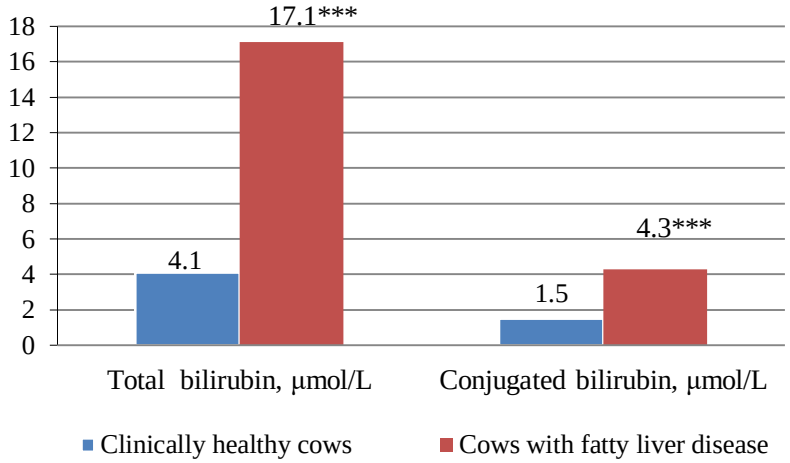

Fig. 5. The content of total and conjugated bilirubin in the blood serum of cows.

At the same time, the cholesterol content in the serum of sick cows decreased by 38% ($P<0.001$), compared to clinically healthy animals (Fig. 6).

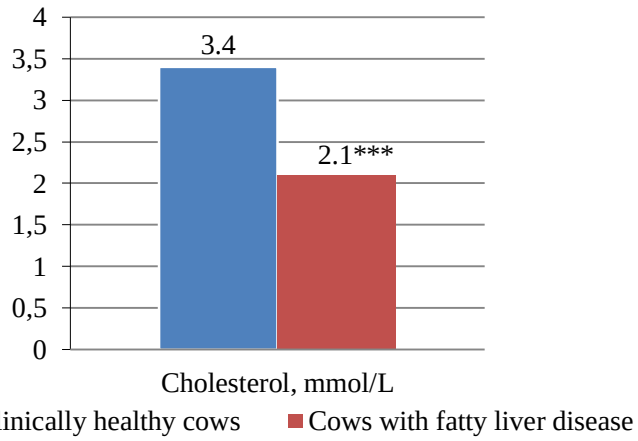

Fig. 6. The cholesterol content in the blood serum of cows.

Discussion

The leading causes of fatty liver disease in cows were the diet imbalance by essential nutrients (excessive protein nutrition, deficiency of metabolic energy, sugar, and crude fiber), poor feed quality, year-round stall keeping of animals. Lack of sugar, the low ratio between easily digestible carbohydrates and digestible protein, and other feeding factors cause metabolic disorders in cows. Sugar deficiency in the diet enhances gluconeogenesis, mobilization of fats from the depot, and their accumulation in the liver (Ingvartsen, 2006; Smith et al., 2017).

Clinically, fatty liver disease was characterized by general and nonspecific symptoms (decreased productivity, weight loss, loss of appetite, hypotension of the rumen, reticulum, and omasum), and the development of typical symptoms (jaundice, pain, and enlargement of the liver) is registered in isolated cases and severe pathology. Therefore, it is vital to conduct laboratory blood tests (Kalaitzakis et al., 2010; Simonov & Vlizlo, 2015; Shcherbatyy et al., 2017). Fat infiltration of hepatocytes and their death due to significant fat accumulation causes a violation of essential liver functions. One of the most critical functions of the liver is protein synthesis. In particular, 100% of albumins is formed in hepatocytes. Therefore, the low content of albumins in cows with fatty liver disease indicates a violation of the protein synthesis function of the liver, as pointed out by other scientists (González et al., 2011; Gutyj et al., 2017; Chernushkin et al., 2020). Given that albumins perform essential functions in the body, including maintaining colloid-osmotic blood pressure, transporting carbohydrates, lipids, hormones, vitamins, minerals, hypoalbuminemia is a negative informative clinical and diagnostic sign of acute and chronic liver failure.

The increase of total protein content established by us in cows with fatty liver disease is often registered in chronic lesions of the body, including hepatodystrophy (Vlizo & Lewtschenko, 1992). This is because in the blood of sick animals increases the content of coarsely dispersed proteins, especially gamma and beta globulins. Excessive globulins production in cows with fatty liver disease may be due to irritation of immunocompetent cells of the mononuclear system (Morris et al., 2009). An increase in the content of globulins and a decrease in albumins in the blood of cows causes dysproteinemia, which is characterized by a decrease in the albumin-globulin ratio.

In addition to synthesis, the role of the liver in protein breakdown is essential. Amino acids formed due to protein proteolysis undergo deamination, which occurs mainly in the liver (Simonov & Vlizlo, 2016). The formation of ammonia accompanies the deamination of amino acids. Ammonia is a toxic substance hazardous to the brain. Ammonia is neutralized in the liver by converting it to urea. Impaired urea formation is manifested by an increase in the level of ammonia in the blood, a decrease in urea content in the blood, and a decrease in its daily excretion in the urine. It should be noted that this function of hepatocytes is relatively stable, so its violation indicates significant changes in the liver parenchyma. This has been established in cows with a severe course of fatty liver disease with hepatic encephalopathy and hepatic coma syndromes (Vlizlo, 1998).

The liver is the main organ that provides a constant glucose content in the blood due to the processes of synthesis and breakdown of glycogen and gluconeogenesis (Simonov et al., 2016). We established that hypoglycemia in cows with fatty liver disease promotes the activation of glycogenesis and the formation of glucose from the glycogen of the liver and muscles. However, glycogenolysis is rapidly extinguished because, in hypoglycemia, glycogen stores are only enough for a few days (Van Knegsel et al., 2007). The body tries to eliminate hypoglycemia through gluconeogenesis. Hypersecretion of glucocorticoids causes the mobilization of fats from the depot, which, entering the liver, causes fatty infiltration of hepatocytes (Morris et al., 2009; Caixeta & Omontese, 2021). Such changes in the body of cows are significant in the pathogenesis of fatty liver disease.

A characteristic organic component of bile is bile acids formed in the liver from cholesterol extracted from high-density lipoproteins (Esteller, 2008; Boyer, 2013). Bile acids carry out adequate enterohepatic circulation in the body due to healthy animals, only 1% of which enter the peripheral blood (Boyer, 2013). It should be noted that the high content of cholates was registered by us in the blood of all sick animals, even though their synthesis occurs in the liver. This may be explained by a decrease in the conjugation and excretion of bile acids by hepatocytes from the bile capillaries into the bile ducts (Rehage et al., 1999). Perhaps that is why our studies of the content of serum bile acids in cows with the fatty liver disease showed a significant ($P<0.001$) increase.

Liver damage in cows caused decreased serum cholesterol, which may be due to reduced esterification of its esters by hepatocytes. Low serum cholesterol content is a characteristic feature of negative energy balance (Gross et al., 2021) when active lipomobilization and liver infiltration develop. Hepatocytes play a leading role in regulating the level and ratio of free and esterified cholesterol (Kraft & Dürr, 2005). Liver disease disrupts hepato-enteral circulation and increases the synthesis of bile acids from cholesterol, which can also cause a decrease in blood cholesterol levels (Chen & Suruga, 2005; Vlizlo & Prystupa, 2011; Lychuk et al., 2016; Lukashchuk et al., 2020). Given that cholesterol is used to synthesize bile acids, corticosteroid hormones, vitamin D are part of cell membranes, its deficiency in sick cows can be regarded as one of the pathogenetic factors of secondary pathologies (Yuskiv & Vlizlo, 2014).

A study of the blood serum in cows with the fatty liver disease showed an increase in total and conjugated bilirubin. The accumulation of bilirubin in the blood of sick animals indicates a violation of its main metabolic processes in the liver − the formation, absorption, conjugation, and excretion in the bile, which is characteristic of fatty liver disease (Kalaitzakis et al., 2010). Thus, in the blood of cows with the fatty liver disease increases the content of total and conjugated bilirubin and bile acids but decreases – cholesterol. Since these are the main components of bile, it can be regarded as a violation of bile production and bile secretion in sick cows. Significant hyperbilirubinemia, which was established in some sick cows, caused jaundice of the mucous membranes.

Conclusion

In cows with fatty liver disease is characterized by disorders of protein synthesis function (decrease of albumin content in the blood serum), bile production, and bile secretion function (decrease in the blood serum of total cholesterol content; an increase of total and conjugated bilirubin, bile acids), urea formation function (decrease of urea content in the blood serum) and carbohydrate function (decrease of glucose content in the blood) of the liver.

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