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Review scientific paper

PATHOGENESIS OF LAMINITIS IN DAIRY COWS

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Summary

The lameness is the earliest but also the most important clinical symptom of the achropodium diseases in cattle. According to literary data, in 90% of cases, the cause of lameness is localized in the hooves, and in 10% of cases it is in other anatomical parts of the limb. In 88% of cases, the pathological process has been manifested at the hind limb. Laminitis is an aseptic inflammation of the corium of the hooves. In addition to the mechanical overloading of the hooves, the toxic causes are also addressed as the causes of this disease. Longer feeding with rapidly digested concentrate, rumen acidosis, sudden change of food components, especially diet with green barley, oat, freshly harvested young legumes and nutrition with molded food, can lead to laminitis. Laminitis is often the result of impact of a large number of factors, such as metabolic and digestive disorders, calving stress, mastitis, metritis, abomasal displacement, bedding without or with very little straw, inability to move, obesity and poor diet. The ration that leads to acidosis also leads to laminitis. Such a ration is difficult to correct in a case when the carbohydrates are present in highest percentage. Vasoactive substances (histamine), which enter the bloodstream from rumen, are considered to lead to damage of the hoof corium. Metabolic disorder is caused by a low pH of rumen, which leads to pathophysiological disorders, which eventually result in the ischemia of the hoof corium and clinically manifest laminitis (leg disposal due to pain, and sometimes forced lying). In addition to histamine and bacterial endotoxins, milk acids and

other biologically active substances are believed to contribute to the onset of this disease. The application of basic principles of the nutrition of the lactating cows can prevent the appearance of laminitis and therefore the appearance of economic losses due to lameness.

Key words: lactating cows, laminitis, pathogenesis.

INTRODUCTION

An intensive cattle breeding includes numerous technological procedures that should provide sustainable production and optimal use of production capacity. Metabolic disorders in high yielding dairy cows, such as ketosis, fatty liver syndrome, puerperal paresis, rumen acidosis and laminitis are caused by a large number of factors, including non-balanced diet and poor breeding conditions. The prophylaxis of metabolic disorders may be done by nutrition, which should be in accordance with the production diet and category of animal combined with the cow's health control (Šamanc et al., 2005).

Laminitis is an aseptic inflammation of the hoof corium (Panousis and Karatzias, 1999; Bojkovski et al., 2000; Radojičić et al., 2017). In addition to the mechanical overloading of the hoof, the toxic agents as well as allergic reaction, may cause this disease (Bojkovski et al., 2007; Bojkovski et al. 2011a). Longer feeding with rapidly digested concentrate, rumen acidosis, sudden change of food components, especially diet with green barley, oat, freshly harvested young legumes and nutrition with molded food, can lead to laminitis (Radojičić et al. 2008). Laminitis is often the result of the impact of a numerous factors such as metabolic and digestive disorders, calving, stress, mastitis, metritis, bedding without or with very little straw and inability to move, obesity and poor diet (Radojičić et al., 2008; Radojičić et al., 2017; Bojkovski et al., 2013). Vasoactive substances (histamine) that enter the bloodstream from rumen are considered to provoke the damage of the hoof corium (Šamanc et al., 2005). Metabolic disorder may be caused by a low pH of rumen, which leads to pathophysiological disorders, which eventually result in the ischemia of the hoof corium and clinically manifest laminitis (leg disposal due to pain, and sometimes forced lying). In addition to histamine, bacterial endotoxins, milk acid and other biologically active substances are believed to contribute to the onset of this disease. The amount of concentrates in ration, occasionally low rumen pH and the appearance of locomotor disorders have a common ethiopathogenetic background (Peterse, 1996; Radojičić et al., 2017).

The role of rumen acidosis in the etiology of laminitis

Following factors are involved in the etiology of rumen acidosis: a large amount of acidic voluminous feeds with low acidogenic value compared to the high content of high quality fiber, an unbalanced ratio between rapidly digested carbohydrates and voluminous nutrients and a large amount of concentrates containing significant amounts of rapidly digested carbohydrates (Šamanc, 2009; Radojičić et al., 2017). It has been found that pH 3.9-4.5 blocks histaminesis, which is active only when pH is neutral or poorly alkaline. In this case, acidosis is very quickly complicated by the histamine intoxication. Histamine increases the permeability of mucous membranes, so it passes into the blood. As already known, histamine can cause decrease in blood pressure and collapse. In severe rumen acidosis, cases of coma are described, with animals lying with front legs raised and head bent toward the chest (Linford, 1990; Garry, 1990). In addition to histamine intoxication, those cows also express acetylcholine intoxication. In the acidic environment, acetylcholine is more stable, and holinesterase is inactive, so the concentration of endogenous acetylcholine that originate from the rumen content is increased. The process develop quickly as in the case of anaphylactic shock, due to the synergistic action of histamine and acetylcholine, while in the rumen acidosis there is action of endogenous and exogenous histamine and acetylcholine. At the beginning of the disease, the increased rumen motility occures, but thereafter the paralysis and paralysis of the rumen walls, or completely ceases of the rumen activity occurs (Owens et al., 1998; Bojkovski et al., 2000).

Acidosis, caused by the accumulation of lactic acid in excess, is a fermentative disorder, which may be expressed in several forms, depending on the level of the imbalance. Basically, rumen acidosis occurs because of consumation of rapidly digested carbohydrates, i.e. when hay is quickly broken down in the rumen under the influence of microorganisms. A decrease in the rumen pH value from 6.8 to 5 inhibits certain groups of microorganisms (protozoa and Gram-negative bacteria), and promotes the development of those bacteria that require an acidic environment. Thus, for example, the presence of a greater number of *Streptococcus bovis* and *Lactobacillus sp*., microorganisms that produce lactic acid, further decrease acidity. If the animal is on this type of diet or energy feed for a long time, acidosis can lead to damage to the lining of the rumen, which allows bacteria to develop ruminitis. Complications, such as peritonitis, liver damage caused by the transfer of infectious agents into the bloodstream, and subsequently laminitis, arise. Less important symptoms can arise, like a simple refusal of food, which later continues into overeating, which can lead to atony of the rumen and accumulation of excess

fluid in the rumen. This, together with the excess fluid in the rumen, results in signs such as dehydration, reduced appetite, reduced milk production, reduced rumen contractions, occasionally dry manure, which can continue into diarrhea. The goal should be to ensure, during prevention, a balance between microorganisms. This can be achieved by offering specific amounts of food given at regular intervals, avoiding sudden changes towards high energy diets. Adequate amounts of concentrate and high quality forage are necessary to achieve these goals (Bojkovski et al., 2000; Bojkovski et al., 2007; Šamanc, 2009; Radojičić et al., 2008; Radojičić et al., 2017).

The role of nutrition in the pathogenesis of laminitis

The main goal related to high-yielding dairy cows nutrition is to ensure, first of all, good health and adequate condition of the animal that should be in lactation about 300 days. Also, cow should deliver a healthy and vital calf once annually, have a numerous of lactations during lifespan as well as the maximum amount of milk with an optimal chemical composition (Radojičić et al., 2008; Đorđević Marković et al., 2009). In order for a high-yielding dairy cows to be able to respond to those demands, the breeding, health conditions, and, above all, nutrition, must be adjusted to the cow's needs (meaning that nutrition should be adjusted to milk production) and brought to the limit of the ideal, within the possibilities of modern cattle farming (Radojičić et al., 2008; Radojičić et al., 2017). Mistakes that are done in the last three months of pregnancy become clearly visible and expressed during the puerperium. The most common mistakes that can occur are various forms of technopaties, among which the most significant is ketosis. From a metabolic point of view, ketosis is a disorder of carbohydrate and fat metabolism, in which β-oxidation of fatty acids is blocked, and the process stops at the level of acetyl-CoA. Oxaloacetate represents the crucial intersection of many pathways in intermediary metabolism, including glucose resynthesize and fatty acid breakdown. Given that the process of glucose synthesis is maximally activated, the largest amount of oxaloacetate is "captured" and "conducted" through gluconeogenesis. This leads to the accumulation of a larger amount of acetyl-CoA, which cannot be fully oxidized. Thus, two acetyl-CoA molecules join together and the synthesis of the first ketone body, acetoacetic acid, occurs and consequently synthesis of both β-oxybutyric acid and acetone. Synthesis of ketone bodies, within physiological limits, also occurs in healthy animals at an intensity of 25 μg/h. Most tissues are able to use ketone bodies as a source of energy, and the degree of their decomposition is proportional to the concentration in the blood up to the level of 3.44 mmol/L. Ketone bodies accumulate in excess in the blood, and are then excreted in urine and milk, and to

a lesser extent through the lungs. By excreting ketone bodies, the body, which is already in an energy deficit, additionally loses a large amount of energy. About 75% of the energy value of fat is bound in ketone bodies.

Summarizing the above considerations, it is necessary to focus on nutrition, which stands out for its importance in the prophylaxis and therapy of this metabolic disorder. Subclinical ketosis can also be monitored by metabolic profile parameters control, which include some analyses to assess the function of liver cells (glucose concentration, AST activity, total bilirubin and albumins). With a valid interpretation of the obtained analyses, it is possible to protect the liver with hepatoprotective agents and prevent ketosis (Radojičić et al., 2008; Radojičić et al., 2017; Šamanc, 2009).

The extremely high needs of high-yielding dairy cows require a larger amount of concentrates with a consequent reduction in the crude fibres content in feed. In order for the ration to be able to meet the nutritional requirements of the animal in production, it is recommended to avoid forage with high water content (silage with less than 25% DM, cellulosic feeds). Due to the excessive voluminousness of such nutrients, i.e. the small amount of energy and nutrients per unit mass, the cow is not able to consume a sufficient amount of food to satisfy basic needs (Radojičić et al., 2008; Radojičić et al., 2017, Šamanc, 2009). Good and high-quality hay (meadow and alfalfa hay as well as mixtures) stands out as the feed of choice, which can be given *ad libitum*, and the concentrated part of the diet, adapted to the production status, should be divided into several parts, in order to achieve a more even use of carbohydrates in the rumen and their decomposition under the influence of microflora. Thus, the possibility of developing rumen acidosis with all its consequences is avoided or significantly reduced. This type of feeding avoids the occurrence of "peaks" of glycemia, which is usual when high-yielding dairy cows are fed with concentrates (Šamanc et al., 2005; Bojkovski et al., 2000; Radojičić et al., 2017).

A special issue in nutrition plan is harmonizing the ratio of different types of carbohydrates that the animal consumes. It is necessary to emphasize the importance of cellulose, but also starch, as a precursor of propionic acid as a key mediator of gluconeogenesis, while the participation of rapidly digested carbohydrates, although they represent "instant energy", carries with it a constant risk of metabolic disorders.

An important parameter is the daily food consumption, which is especially an issue during stress and dramatic physiological changes that occur during late pregnancy, parturition and early lactation. In general, the diet should be tasty, with preserved organoleptic properties, hygienically correct and without harmful contaminants.

The nutrition control includes short-term control (pH of rumen contents, amount of volatile fatty acids and levels of some hormones such as insulin, glucagon, gastrin) and long-term control of consumption (physiological state, nitrogen status, environmental factors, photoperiodicity and seasonal differences, level of production and total energy needs). Cow body mass, genetic basis, health status, competitive instincts of higher priority (thermoregulation), as well as factors related to the palatability of the diet are also important.

In conditions of unbalanced nutrition in the prepartal period, excess nutrients are stored in body and the so-called "fatty liver syndrome" occurs. In conditions of energy deficit and the consequent accelerated fat mobilization from the body stores, which is a frequent in obese cows, the accumulation of free fatty acids in the blood and liver occurs. A high concentration of free fatty acids in the blood causes a appetite depression, which means that the animal reduce consumption, which then leads to an energy deficit, when cows suddenly lose weight, with a possible fatal outcome. Accumulation of fatty acids occurs in the liver in the form of fatty infiltration or degeneration of hepatocytes. With such an additional load, the liver loses its activity, which contributes to the emergence of ketosis, meaning that the reparation and restitution processes in hepatocytes are hindered, since healing is achieved only when the liver is free from excess fat, which is a slow and long-term process (Šamanc, 2009; Radojičić et al., 2017). "Fatty liver syndrome" is an example of an energy imbalance caused by excessive food/energy consumption and increased fat deposition in hepatocytes, but also in other tissues such as subcutaneous tissue. Therefore, the term "fat cow syndrome" is often used. When a cow receives high-energy diet during the late lactation and the dry period, fat storage occurs. This condition leads to difficult calving, placental abruption or even the occurrence of metritis. When a loss of appetite occurs, there is an accelerated mobilization of fat from the body's stores and, consequently, there is an increased ketone bodies synthesis. Herds with this diet have fertility problem, which is reflected in long service periods and reduced conception (Đoković, 2010). Herds with long intervals between calving usually have obese cows at the time of calving (Radojičić et al., 2008). Ketosis is one of the secondary diseases that occur in these conditions. In order to diagnose subclinical ketosis, it is necessary to obtain a metabolic profile at least twice a year in cows that are in late pregnancy and in early lactation (Radojičić et al., 2017). The goals to be achieved, in order to prevent fatty liver syndrome, are the provision of adequate, not highly energy-rich diets, in order to prepare the rumen microorganisms for the diets that will be offered during lactation. This means that dry cows should receive 2-3 kg of these nutrients two weeks before calving. After calving, the concentrate should be increased by 1 kg/day, until peak

of lactation is reached. It is necessary to offer to cows 2-4 kg of hay per day, in order to reduce the fluctuation of microorganisms, which can occur during changes in the concentrate content in diets, as a result of high needs in the early period of lactation. Interval between calving should be from 12 to 13 months, meaning year/calf. Also, it is necessary to separate dry from lactating cows in order to reduce occurrence of "fatty liver syndrome" and to maintain high lactation (Đorđević Marković et al., 2009; Radojičić et al., 2008; Radojičić et al., 2017).

Cows fed rations with a high content of easily soluble proteins (17% protein with 75% solubility) may require more inseminations and may have prolonged cycle between calving. This is called infertility syndrome. As a consequence of this diet, rumen has a high content of ammonia, which is excreted through urine or milk. Ammonia ion in excess has a toxic effect on the embryo and prevents implantation and development of the fetus. Therefore, it is necessary to avoid a diet with high amounts of protein, especially easily soluble proteins, and provide the necessary amounts of energy with a balanced protein:energy ratio (Đorđević Marković et al., 2009; Radojičić et al., 2017).

The requirements of microorganisms in amino acids and energy, as well as the range of pH in the rumen (from 5.5 to 6.8) should be taken into account when determining the best ration for high-yielding dairy cows. Prevention implies a balance between microorganisms, which can be achieved by offering certain amounts of food at equal intervals, and avoiding sudden changes to high-energy diets. Adequate quantities of concentrates and high quality forage are necessary to achieve these goals (Nocek, 1997; Đorđević Marković et al., 2009; Radojičić et al., 2017).

As a consequence of a mineral metabolism disorder (insufficient intake or increased loss) a pareperal paresis, also known as hypocalcemia or milk fever, occurs. The decrease in calcium levels (hypocalcemia) in cows with a puerperal paresis is associated with general weakness, "inability to rise up", sometimes followed by a coma and death, if this disorder is not treated on time. In cows with a puerperal paresis, there are also disorders like indigestion and reduced absorption of nutrients. The factors that contribute to the onset of hypocalcemia, like a decreased mobilisation of calcium from bone or absorption from small intestine in older cows, and the postpartal reduction of the appetite, further complicate this problem (Radojičić et al. 2017; Nedić et al., 2023).

Dysbalance of minerals immediately after calving, in older high-yielding dairy cows, usually leads to so-called typical hypocalcemia, but also to atypical puerperal paresis, which is dominantly characterized by decreased phosphorus levels, and/or less often to the "Downer cow syndrome " (Nedić et al., 2023).

Prophylaxis and recommendations also relate to the breeding and feeding cows during

dry period. Because of this, up to three weeks before calving the high-yielding dairy cows should be gradually prepared to get used to the lactation cow's diet, in order for the rumen microorganisms to "prepare and develop" for the conditions of a new diet. Also, an equal ratio or even more phosphorus than calcium should be given in the diet before drying cows, in order to start a calcium mobilisation from stores (Đordjević Marković et al., 2009). It is also possible to prepare an acid or anion diet. Such a diet reduces the appearance of milk fever through a certain acidification, which maximizes the ionization of calcium in the guts, improves its absorption, and improves the transportation of calcium from the bones. Another measure that can be taken, if the term of the calving is known, is a vitamin D supplementation. The frequent vitamin D supplementation is not advisable, especially in the form of the injection, because vitamin D has a structure and catabolism similar to steroid hormones, which can affect the hepatocytes, which are significantly damaged in high-yielding dairy cows fed with unbalanced diets (Radojičić et al., 2017).

Diets with low calcium level, few weeks before calving, may prevent puerperal paresis by prepartal activation of the bones and intestinal channels. It is recommended that the two weeks before calving, diet with less than 80g Ca, 60g P and about 35,000 IU of vitamin D should be applied. It is very important to solve the issues related to choosing of diets with poor calcium levels and composing an adequate diet, which meets the requirements of the animal in the last weeks of dry period. Potatoes and its by products as well as other root and tuber crops, brewer's spent grain, corn germ meal, bran and wheat flour are nutrients of choice. Immediately after calving, when it is necessary to offer animals a diet rich in calcium, tail noodles, hay and silage (meadow and alfalfa hay), as well as the addition of mineral nutrients as a source of calcium are used. A practical disadvantage of such a diet regime is the need to gradually change a diet after calving, because it is known that sudden diet change can cause a disorder of microorganisms and lead to rumen acidosis. Practical experiences show that there are cases of puerperal paresis on some farms without pronounced hypocalcemia, but with serious hypomagnessiamia. Magnesium deficiency is shown as a significant etiological factor in the emergence of puerperal paresis, disrupting calcium homeostasis, because it reduces the degree of mobilization of calcium after calving, and given that the mobilization of magnesium from the stores is much slower than the mobilization of calcium, there are often symptoms that seemed like grass tetany (Linford, 1990; Peterse, 1996; Radojičić et al., 2008; Radojičić et al., 2017).

Patogenesis of laminitis

As one of the important predisposing factors of the etiology and pathogenesis of laminitis, especially at the beginning of the disease, is the anatomical characteristic of the blood vessels of the corium, which is narrowed between the phalangeal bone and the corium of hoof. In such a fulfilled space, there is limited expansion in the case of fluid leaking into the interstitium. This is one of the earliest disorders of the hoof corium vascular elements caused by histamine. Increased transudation and exudation increase tissue pressure that further complicates blood circulation in the laminae and causes their ischemia. This is a result of the inelasticity of the cornea, which cannot expand under the pressure of the swelled hoof corium. In this phase, laminitis is accompanied with increased temperature and pain of the affected hoof, as well as with a high degree of lameness from the very beginning of the disease. The laminae of the hoof, about 1,300 in each hoof, are narrow and very soft in structure. They are well supplied with blood and there are many arteriovenous anastomoses in them. A rich network of nerve plexuses spreads in the corium tissue, because, as is known, hooves are not only mechanical support for the body, but are a specific tactile organ (maintaining balance and movement). Other factors that have been mentioned, such as body weight, nutritional status, genetic and acquired anomalies, may play a certain role in the pathogenesis of aseptic pododermatitis. Circulation disorders, ischemia and hypoxia, cause degenerative changes in the corium and lamina. When the process takes a chronic course, there may be a change in the position of the phalangeal bone, deformation of the hooves and the protrusion of the tip of the bone through the sole of the hooves. These are mechanical damages due to the lamina corium pressure, disturbances in circulation and necrosis. Related to this, there are numerous changes that occur later, such as thickening of the sole of the hoof (double sole), bleeding in the sole, sometimes the appearance of blood bruises. In some cases, changes in the color of the soles characterize this process. Pale areas often interspersed with hyperemic fields or numerous hemorrhages are observed (Šamanc et al., 2005; Bojkovski et al., 2011b; Radojičić et al., 2008; Radojičić et al., 2017). Prophylactic measures aimed to prevent production diseases in high-yielding dairy cows should primarily enable the physiological activity of the rumen microorganisms at the moment when the dry cow enters lactation. Balanced diet according to the production ration is required, as well as separation of dry from lactating cows and regular control of the metabolic profile. It is also important to feed dry cows with a sufficient amount of forage at least two weeks before calving (Ivanov et al., 2005; Đoković, 2010).

CONCLUSION

Laminitis is an aseptic inflammation of the corium of the hooves. In addition to mechanical overloading of the hooves, the toxic causes are also addressed as the causes of this disease. Longer feeding with rapidly digested concentrate, rumen acidosis, sudden change of food components, especially diet with green barley, oat, freshly harvested young legumes and nutrition with molded food, can lead to laminitis. Laminitis is often the result of impact of a large number of factors, such as metabolic and digestive disorders, calving stress, mastitis, metritis, abomasal displacement, bedding without or with very little straw, inability to move, obesity and poor diet. The ration that leads to acidosis also leads to laminitis. Such a ration is difficult to correct in a case when the carbohydrates are present in highest percentage. Vasoactive substances (histamine), which enter the bloodstream from rumen, are considered to lead to damage of the hoof corium. Metabolic disorder is caused by a low pH of rumen, which leads to pathophysiological disorders, which eventually result in the ischemia of the hoof corium and clinically manifest laminitis (leg disposal due to pain, and sometimes forced lying). In addition to histamine and bacterial endotoxins, milk acids and other biologically active substances are believed to contribute to the onset of this disease. The application of basic principles of the nutrition of the lactating cows can prevent the appearance of laminitis. Great importance is given to the use of mineral substances with a buffering effect on the electrochemical reaction of rumen contents.

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