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THE ROLE OF ACUTE PHASE PROTEINS IN THE PATHOGENESIS OF METABOLIC SYNDROME IN OBESE HORSES

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The aim of our research was to establish reference values for acute-phase proteins during obesity in horses. The study was conducted on 20 horses aged 5–10 years. The control group included 10 animals with a body condition score (BCS) of 4–6 according to the Henneke scale, while the experimental group consisted of 10 horses showing signs of obesity (≥7 BCS).

The serum concentrations of circulating immune complexes (CICs), seromucoids, C-reactive protein (CRP), haptoglobin, total protein, and its fractions were measured. It was found that the biochemical analysis of serum revealed statistically significant changes in protein metabolism in obese animals. The total protein level in the experimental group was 75.0 (71.5–76.5) g/L compared to 65.5 (61.8–72.0) g/L in the control group ($p<0.05$), indicating increased protein synthesis. This increase was due to a rise in globulin levels to 39.5 (37.8–42.0) g/L compared to 32.0 (30.5–36.0) g/L in the control group ($p<0.001$), while albumin levels remained unchanged (30.5±1.2 g/L in the experimental group and 30.1±1.1 g/L in the control group, $p>0.05$).

Among acute-phase proteins, the CRP level in obese horses was 5.62 (4.98–5.92) mg/L, exceeding the values in the control group (3.19 (3.08–3.63) mg/L, $p<0.01$). Seromucoids increased by 37.8% (3.21 (3.11–3.61) g/L compared to 2.19 (2.06–2.26) g/L, $p<0.001$), and haptoglobin concentration reached 0.617 (0.581–0.678) g/L compared to 0.462 (0.429–0.477) g/L in the control group ($p<0.001$). The level of CICs in the experimental group was 160.0 (138.8–170.0) mmol/L, significantly exceeding the values in the control group (116.0 (99.5–129.0) mmol/L, $p<0.001$). The albumin-to-globulin ratio decreased from 0.74 in the control group to 0.61 in the experimental group ($p<0.01$), indicating a predominance of the globulin fraction associated with chronic inflammation.

We believe that the mechanism of these pathological changes is related to obesity in animals and, possibly, to laminitis, the development of which is one of the pathogenic links in metabolic syndrome.

Keywords: obesity, metabolic syndrome, inflammation, acute phase proteins, laminitis.

РОЛЬ БІЛКІВ ГОСТРОЇ ФАЗИ ЗАПАЛЕННЯ В ПАТОГЕНЕЗІ МЕТАБОЛІЧНОГО СИНДРОМУ ПРИ ОЖИРІННІ У КОНЕЙ

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Метаболічний синдром та ожиріння у коней є тісно пов'язаними між собою процесами, котрі супроводжуються хронічним запаленням. Метою наших досліджень було встановлення нормативних показників білків гострої фази запалення за ожиріння у коней. Дослідження проведено на 20 конях віком 5–10 років. До контрольної групи увійшли 10 тварин із оцінкою стану тіла 4–6 балів за шкалою Хеннеке, а до дослідної групи – 10 коней із ознаками ожиріння (≥7 балів).

В сироватці крові визначали концентрацію циркулюючих імунних комплексів, серомукоїдів, С-реактивного протеїну, гаптоглобіну, загального білку та його фракцій. Встановлено, що біохімічний аналіз сироватки крові виявив статистично значущі зміни у показниках білкового метаболізму у тварин із ожирінням. Рівень загального білка у дослідній групі становив 75,0 (71,5–76,5) г/л проти 65,5 (61,8–72,0) г/л у контрольній ($p<0,05$), що вказує на підвищення синтезу білків. Підвищення було зумовлено зростанням рівня глобулінів до 39,5 (37,8–42,0) г/л у порівнянні з 32,0 (30,5–36,0) г/л у контрольній групі ($p<0,001$), тоді як рівень альбумінів залишався без змін (30,5±1,2 г/л у дослідній групі та 30,1±1,1 г/л у контрольній, $p>0,05$). Серед білків гострої фази запалення рівень С-реактивного протеїну у тварин із ожирінням становив 5,62 (4,98–5,92) мг/л, що перевищувало значення контрольної групи (3,19 (3,08–3,63) мг/л, $p<0,01$). Серомукоїди зросли на 37,8 % (3,21 (3,11–3,61) проти 2,19 (2,06–2,26) г/л., $p<0,001$), а концентрація гаптоглобіну досягла 0,617 (0,581–0,678) г/л порівняно з 0,462 (0,429–0,477) г/л у контрольній групі ($p<0,001$). Рівень циркулюючих імунних комплексів (ЦІК) у дослідній групі становив 160,0 (138,8–170,0) ммоль/л., що значно перевищувало показники контрольної групи (116,0 (99,5–129,0) ммоль/л., $p<0,001$). Альбумін-глобулінове співвідношення зменшилося з 0,74 у контрольній групі до 0,61 у дослідній ($p<0,01$), що вказує на переважання глобулінової фракції, пов'язаної з хронічним запаленням.

На нашу думку механізм розвитку цих патологічних змін пов'язаний як із ожирінням у тварин, так і, можливо, із ламінітом, розвиток якого є однією із патогенетичних ланок метаболічного синдрому.

Ключові слова: ожиріння, метаболічний синдром, запалення, білки гострої фази, ламініт.

Obesity of horses on the background of metabolic syndrome is characterized by metabolic disorders, which can lead to serious consequences for animal health, especially with a sedentary lifestyle or overeating (Carter R. A. et al., 2010). According to research, a certain proportion of horses are overweight, which increases the risk of developing obesity and metabolic syndrome. Some researchers believe that the etiology and pathogenesis of obesity and the development of equine metabolic syndrome is similar to that of humans, and includes insulin resistance, hyperglycemia, hyperlipidemia, and

hypertension (Morgan R. et al., 2015). The pathogenesis of metabolic syndrome involves a complex interaction between hormonal, metabolic, and inflammatory processes (Durham A. E. et al., 2019). This leads to impaired carbohydrate and fat metabolism, as well as changes in the function of the endocrine system, which can lead to the development of cardiovascular diseases, obesity, laminitis and other diseases (Karikoski N. P. et al., 2011).

The role of acute phase inflammatory proteins in the context of obesity in horses has hardly been studied, although it is known that obesity in horses is often accompanied by chronic inflammation, which plays a key role in its pathogenesis. Acute inflammatory phase proteins are important inflammatory mediators and may be significant indicators of the degree of low-level inflammatory response in obesity. Studying the role of proteins in the acute phase of inflammation will allow us to understand the mechanisms by which obesity affects the metabolism and health of horses. They can be important biomarkers for diagnosing and assessing the severity of obesity in horses, as well as monitoring the effectiveness of therapy (Menzies-Gow N. J. et al., 2017).

Acute inflammatory phase proteins are a group of proteins that are actively synthesized in response to various stressors, such as injuries, infections, tumors, and other pathological conditions (Bilous L. L. & Kovalchuk N. A., 2015) and can affect various organs and tissues, including adipose tissue, liver, and muscle, leading to impaired energy balance and the development of obesity characteristic of metabolic syndrome. They perform a number of important functions, such as regulating the immune response, correcting metabolism, protecting against infections, and forming a response to tissue remodeling, antiviral protection, phagocytosis, regulating apoptosis, and other processes related to protecting the body from harmful influences (Slivinska L. G. et al., 2017). According to the literature, these proteins (APP) are key elements of the innate immune system and are part of the acute phase response (APR). These proteins are mainly synthesized by hepatocytes, and their production depends on cytokines. The main inducers of these proteins are interleukin-6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor alpha (TNF-α). As a rule, the reaction is non-specific and is associated with infection, injury, or inflammation. However, other conditions, such as heat stress , childbirth, and intense exercise, have been associated with changes in app levels in animals (Zak, A., 2020). Acute phase proteins, in addition to immune responses, are actively involved in the body's inflammatory response and can be synthesized by cells, including hepatocytes, monocytes, macrophages, fibroblasts, etc. It is also important that inflammatory proteins can also be involved in the formation of inflammatory complexes, protein complexes that play a key role in triggering the body's inflammatory cascade response. The group of these proteins includes proteins whose concentration in the blood serum during inflammation increases or decreases by at least 25 percent [Gołda R. et al., 2004]. Such proteins are called positive or negative, respectively. Positive factors include: C-reactive protein(CRP), fibrinogen, haptoglobin, ceruloplasmin, a number of complement factors, as well as numerous proteinases and their inhibitors (Tkaczenko, H., 2023). Negative reactants include prealbumin, albumin, and transferrin (Carter, R. A., 2010). According to the literature, the synthesis of acute phase proteins in the liver in conditions of obesity contributes to the activation of the connective tissue system and the progression of fibrosis without the development of classical steatohepatitis. In addition, factors of the hemostatic system are activated with the development of hypercoagulation syndrome and the progression of dyslipidemia (Ranganathan S., 2001).

Thus, based on the functions of these proteins and their role, the aim of the study was to determine the content of proteins of the acute phase of inflammation in horses in normal and obese conditions.

Materials and methods. Studies were conducted on twenty horses of different breeds and sexes, from which age-appropriate groups were formed: clinically healthy animals (n=10) and a control group with signs of obesity (n=10). Mostly horses were of the Ukrainian riding breed, and partly local on its base. The body condition of each horse was evaluated on a 9-point Henneke scale according to a visual examination of the animals by a veterinarian.

The conditions of feeding and keeping animals met physiological needs. The diet contained the necessary amount of nutrients, and access to water and the ability to walk were free. Regular clinical examination of animals was carried out, including determination of basic physiological parameters and examination of organs and systems using general clinical methods. The control group included clinically healthy animals with normal physiological parameters. The diagnosis of obesity was made according to the Hennecke point system, where the first rank corresponds to exhaustion, and the ninth corresponds to a very fat animal, the assessment was carried out by a veterinary doctor of the farm. Blood was taken from the jugular vein directly into test tubes for further biochemical studies. Blood was taken from the jugular vein on an empty stomach into vacuum tubes with a volume of 10 cm^3 for further preparation of blood serum. In the blood serum, such biochemical parameters as the concentration of Total Protein, albumins, total globulins, haptoglobin and seroglycoids were determined using reagent kits of Prjsc "Reagent" (Ukraine). The concentration of circulating immune complexes was determined as described (Gołda R. et al., 2004), precipitation of protein complexes antigen antibody PEG 6000. Biochemical parameters were recorded on a SHIMADZU UV 1800 spectrophotometer (Japan).

All animal studies were conducted in accordance with the basic principles of Bioethics, in accordance with the European Convention for the protection of vertebrates used for experimental and other scientific purposes (European convention..., 1986), and the "general ethical principles of animal experiments", adopted by the First National Congress on Bioethics (Procedure for conducting..., 2012).

Statistical data analysis was performed using Minitab 19 and Minitab Inc. Based on the results of statistical processing, the tables show nonparametric indicators, such as: median, quartiles Q1 and Q3. A significant difference between the study groups was established based on the calculation of the Mann−Whitney criterion ($p<0.05$).

Results. Detailed results of serum concentrations of circulating immune complexes, seromucoids, reactive protein C, haptoglobin, total protein, and protein fractions are presented in Table 1. however, it should be noted that horses did not have a significant difference between the age of animals of different groups.

In the animals of the experimental group, a significant increase in the point assessment of body condition was recorded to a median indicator of 7.0 ($p<0.05$), which corresponds to the assessment of "well-fed animal". Thus, probable differences between the groups were established for almost each of the studied indicators.

Thus, according to the results of our studies, the level of circulating immune complexes in obese horses was increased by 37.9% and reached the level of 160.0 mmol/l (***$p<0.001$). It should also be noted that the concentration of circulating immune complexes had a significant positive correlation (0.769) with the content of seromucoids, which may be associated with chronic inflammation, which is often observed in obesity.

In this study, we found a 33.5% increase in haptoglobin levels to 0.617 g/l ($p<0.001$) compared to the control group, which may indicate various pathological processes in the body, including impaired liver function, as well as inflammatory processes. In addition, the level of haptoglobin directly correlated with the age of the animals (0.771) and the content of reactive protein C with a content of 0.781.

Table 1

Results of acute phase protein concentration in the control and obese groups

Clinically healthy horses, n=10									
characteristic value	**Age, years**	**Body Condition,** points	**circulating points immune complexes, mmol / L**	**haptoglobin, G / L**	**L C-reactive protein, mg / L**	**Seromucoid, G / L**	**Total Protein, G / L**	**albumins, G / L**	**globulins, G / L**
Median	11,5	6,5	116,0	0,462	3,19	2,19	65,5	34,0	32,0
Q_1	9,75	5,75	99,5	0,429	3,08	2,06	61,8	32,0	30,5
Q_3	12,25	7,00	129,0	0,477	3,63	2,26	72,0	36,0	36,0
Obese horses, n=10									
Median	12,0	7,0*	160,0 ***	0,617 ***	5,62 ***	3,21 ***	75,0*	35,0	39,5 ***
Q_1	12,0	6,75	138,75	0,581	4,98	3,11	71,5	33,3	37,8
Q_3	14,0	8,00	170,0	0,678	5,92	3,61	76,5	36,3	42,0

Notes: - p<0.05, * * - p<0.01, * * * - p<0.001, compared to clinically healthy horses*

We found that the content of reactive protein C increased by 76.2% (p<0.001) and reached a level of 5.62 mg/L.

Also, the development of the inflammatory process in horses of the experimental group is indicated by an increase in the level of globulins by 25.8 % (p<0.001), which was 39.5 g/l against the background of an increase in the level of total protein to 75.0 G/L, which was 14.3% (p<0.05). Moreover, it should be noted that the level of albumins has not undergone significant changes.

These data are supplemented by the albumin-globulin ratio- the ratio of albumin to serum globulin levels, which was 1.42 in healthy horses and 0.89 in obese horses, which was 37.3% (p<0.05).

The results obtained in our study indicate that the content of seromucoids significantly increased by 47.2 % (p<0.001) to the level of 3.21 G/L, compared with the control group.

Discusion. Blood serum is a dynamic equilibrium system that consists of 70.0% proteins, and the specifics of their metabolism reflect the state of almost all body tissues.

Circulating immune complexes can be formed by the interaction of antigens with antibodies in the blood. When these complexes are formed in excessive amounts or cannot be effectively purified by the body, they can trigger an inflammatory response. Inflammation can result from the deposition of circulating immune complexes in tissues,

where they activate inflammatory processes, contributing to tissue damage and the subsequent development of inflammatory diseases (Tkaczenko H. et al., 2023). At the same time, a high level of circulating immune complexes (especially those containing Class G immunoglobulins) stimulates the suppressor activity of T cells (Morgan, R., 2015). In addition, it is known that processes caused by the deposition of circulating immune complexes in tissues can affect metabolism, causing insulin resistance and other factors that contribute to the development of obesity (Stefaniuk-Szmukier M. et al., 2023). The data obtained by US may indicate an increase in low-molecular complexes, since according to the literature, low-molecular circulating immune complexes have the greatest toxicity to body tissues, but the increased level of high-molecular circulating immune complexes can be caused by the processes of activation of functional systems of polymorphonuclear leukocytes and mononuclears, as well as an increase in complement activity, which is a positive shift in the immune system (Slivinska, L. G., 2017).

The next important proteins in the acute phase of inflammation are haptoglobin and C reactive protein. Haptoglobin is a protein that binds free hemoglobin in the blood, preventing its toxic effects. An increase in the level of haptoglobin in the blood can be associated with various physiological or pathological conditions. It is known that haptoglobin in horses is characterized by an increase in peritonitis or after surgery, can be produced by adipocytes and is considered a marker of obesity (Johnson P. J., 2002), and also acts as an antioxidant, reducing cell damage and suppressing inflammation by reducing prostaglandin synthesis.

It is known that the content of reactive protein C in horses increases several times during inflammation and obesity (Girardi F. M. et al., 2019). Reactive protein C concentrations have been shown to increase in enteritis, pneumonia, and arthritis in adult horses and foals. In addition, reactive protein C concentrations correlate with markers of inflammation and increase during experimentally induced laminitis; however, others have shown no differences in reactive protein C concentrations in obese horses (Johnson P. J. et al., 2010). Also, the pathogenesis of increased C-reactive protein against the background of immune system activation leads to the release of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), which is the main factor in triggering this process and tumor necrosis factor (TNF-α) (Witkowska-Piłaszewicz, O. D., 2019).

We found that the content of reactive protein C increased which completely coincides with the studies of previous authors and may indicate both the development of animal obesity and the subclinical course of laminitis with activation of the immune system, which requires further research (Reynolds A. et al., 2019; Zak A. et al., 2020).

Because obesity is accompanied by low-grade chronic inflammation, and fat cells (adipocytes) secrete various pro-inflammatory molecules, in particular cytokines. these inflammatory factors can affect globulin levels because they stimulate the production of acute phase proteins that include certain globulins (Tkaczenko, H., 2023). In turn, an increase in the globulin fraction indicates a disorder of protein synthesis in the liver against the background of metabolic processes (Johnson P. J., 2002). It should also be noted that metabolic disorders - obesity can cause changes in the levels of hormones such as insulin, leptin, cortisol, and others, which affects the production and level of globulins in the blood (Carter, R. A.,.2010). These data are supplemented by the albumin-globulin ratio. A decrease in this ratio can occur in response to inflammation, when the liver directs resources to produce pro-inflammatory proteins (globulins), as well as in the case of chronic diffuse liver and kidney dysfunction (Duncan Jr., 2003).

To differentiate between acute and chronic inflammation, there are discussions about the role of seromucoids: they are indicated, given that they are a fairly sensitive marker of inflammatory processes, during which their level increases several times. An increase in seromucoids has been described in many inflammations of bacterial and viral etiology. according to other data, seromucoids are considered markers of chronic inflammation rather than acute (Galatyuk A. et al., 2018). In addition, normally seromucoids are components of connective tissue, so when it is destroyed, they enter the blood in significant quantities and are therefore considered markers of destructive and degenerative processes (Witkowska Piłaszewicz O. D. et al., 2019). This can also be evidenced by the corresponding correlation data on the direct dependence of the content of seromucoids and the state of the body, circulating immune complexes and haptoglobin and C reactive protein. According to some reports, seromucoids also correlated with body mass index and adipose tissue content (Henneke D. R. et al., 1983), and the level of adiponectin (Gołda R. et al., 2004). Therefore, in our opinion, the content of seromucoids can be used as an integral indicator of proteins of the acute phase of inflammation in horses with obesity.

Conclusions. Obesity in horses leads to a significant increase in the levels of acute phase inflammatory proteins, which can be used as markers of inflammation in clinical practice to assess the intensity of the inflammatory response and prognosis of the disease. Determination of seromucoid concentration can be used as an integral indicator of acute inflammatory phase proteins in horse obesity.

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