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THE ROLE OF ADIPONECTIN, LEPTIN, AND THEIR RATIO IN THE PATHOGENESIS OF OBESITY AND INSULIN RESISTANCE IN HORSES

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Metabolic syndrome in horses is a multifactorial pathological condition characterized by abdominal obesity, insulin resistance, hormonal dysfunctions, and chronic low-grade inflammation. A key aspect in the pathogenesis of this syndrome is the imbalance of adipokines, particularly leptin and adiponectin, which may play a crucial role in the development of metabolic disturbances. The aim of this study was to determine the changes in leptin, adiponectin levels, and their ratio (leptin-to-adiponectin ratio, LAR) in horses with varying degrees of body condition and to evaluate their association with insulin resistance development.

The study involved 18 clinically healthy horses aged 5–10 years, divided into a control group (n=9; body condition score [BCS] 4–6 according to Henneke scale) and an obese group (n=9; BCS ≥7). Serum concentrations of adiponectin and leptin were measured by enzyme-linked immunosorbent assay (ELISA), along with glucose and insulin levels. Insulin sensitivity index (RISQI) and LAR were calculated.

Results demonstrated that obese horses had significantly higher leptin levels ($p<0.001$) and significantly lower adiponectin concentrations compared to controls. This resulted in more than a threefold increase in LAR ($p<0.001$), indicating marked disruption of hormonal regulation of adipose tissue. Additionally, elevated glycemia, hyperinsulinemia, and decreased RISQI values were observed, confirming insulin resistance in overweight horses.

These findings suggest that LAR can serve as a sensitive early biomarker of metabolic distress and insulin resistance in horses. Its use is recommended for early

identification of at-risk animals, monitoring the effectiveness of preventive measures, and substantiating personalized strategies for diet and physical activity modification aimed at preventing complications associated with metabolic syndrome.

Keywords: *horses, obesity, leptin, adiponectin, insulin resistance*

РОЛЬ АДИПОНЕКТИНУ, ЛЕПТИНУ ТА ЇХ СПІВВІДНОШЕННЯ У ПАТОГЕНЕЗІ ОЖИРІННЯ Й ІНСУЛІНОРЕЗИСТЕНТНОСТІ У КОНЕЙ

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Метаболічний синдром у коней є поліетіологічним патологічним станом, що характеризується абдомінальним ожирінням, інсулінорезистентністю, гормональними дисфункціями та хронічним низькоградусним запаленням. Особливу увагу в патогенезі цього синдрому привертає дисбаланс адипокінів, зокрема лептину й адипонектину, який може відігравати ключову роль у розвитку метаболічних порушень. Метою дослідження було визначення змін рівнів лептину, адипонектину та їх співвідношення (leptin-to-adiponectin ratio, LAR) у коней із різним ступенем вгодованості та оцінка їх зв'язку з розвитком інсулінорезистентності.

У дослідженні було обстежено 18 клінічно здорових коней віком 5–10 років, яких розподілено на контрольну групу (n=9; BCS 4–6 за шкалою Хеннеке) та групу з ожирінням (n=9; BCS ≥7). У сироватці крові тварин визначали концентрації адипонектину та лептину методом імуноферментного аналізу, рівні глюкози та інсуліну, а також розраховували індекс чутливості до інсуліну (RISQI) та співвідношення LAR.

Результати показали, що у тварин з ожирінням рівень лептину був статистично достовірно вищим (p<0,001), а концентрація адипонектину — достовірно нижчою порівняно з контролем. Це зумовило понад трикратне зростання LAR (p<0,001), що свідчить про істотне порушення гормональної регуляції жирової тканини. Також спостерігалися підвищення глікемії та гіперінсулінемія, а також зниження RISQI, що є індикатором інсулінорезистентності у коней із надмірною вгодованістю.

Отримані результати свідчать про те, що показник LAR може бути інформативним раннім біомаркером метаболічного дистресу та інсулінорезистентності у коней. Його використання доцільне для раннього виявлення тварин групи ризику, моніторингу ефективності профілактичних заходів та обґрунтування персоніфікованих стратегій корекції раціону та

фізичної активності з метою попередження ускладнень, асоційованих з метаболічним синдромом.

Ключові слова: *коні, ожиріння, лептин, адипонектин, інсулінорезистентність.*

Introduction. A pressing issue today is the development of equine metabolic syndrome (EMS), a term used to describe horses that exhibit a range of problems, including obesity, regional obesity, insulin resistance, and susceptibility to laminitis. Other names originally proposed for this syndrome included peripheral Cushing's syndrome, insulin resistance syndrome, syndrome X, omentum Cushing's syndrome, and central obesity.

The specific aetiology of this syndrome is currently unknown. According to widespread data, genetic predisposition, an unbalanced diet, insufficient physical activity, increased stress levels, chronic inflammation in the body, or a combination of these factors contribute to its development. New data obtained during the study of the pathogenesis of this pathology have made it possible to identify its components: decreased insulin-dependent glucose utilisation by tissues, hyperinsulinemia, hyperglycaemia, hypertriglyceridaemia, low levels of cholesterol, high-density lipoproteins (HDL), microalbuminuria, decreased fibrinolytic activity of the blood, as well as hyperleptinaemia and leptin resistance. It should also be noted that the combination of individual components of the syndrome can be considered within the framework of metabolic syndrome only in the presence of insulin resistance.

There is little epidemiological data on the prevalence of metabolic syndrome, but according to the available literature, it has been established that in different horse populations in the United Kingdom, the pathology occurs in 21% to 45% of animals. In other countries, obesity occurs in 10% of adult Icelandic horses in Denmark, 8%–29% of horses in Canada, 24.5% of Australian riding horses and ponies, and 35% and 51% of adult light breed horses in the United States (Robin C. A. et al., 2015; Wyse C. A. et al., 2008; Harker I. J., Harris P. A. & Barfoot C. F., 2011).

Studies have generally shown that metabolic syndrome in horses is more common in physically inactive animals, and insulin concentration is significantly higher in older horses and ponies compared to younger ones, while adiponectin concentration in the blood is lower in older animals compared to younger ones, which is consistent with the age-related relationship and identification of metabolism. However, gender and seasonality do not affect most markers of metabolic identification in animals (Hart K. A. et al., 2016; Wray H. et al., 2013; Buff P. R. et al., 2002; Kaufman K. L. et al., 2025).

In metabolic syndrome, which is a consequence of insulin resistance, modern researchers pay special attention to the role of visceral adipose tissue in connection with the synthesis and release of various adipokines by adipocytes (Galic S., Oakhill J. S. & Steinberg G. R., 2010; Napoli G. et al., 2023).

Today, scientists recognise that adipose tissue is one of the most important organs in our body, involved in the regulation of many different functions. These include: coagulation, appetite regulation, immune defence, glucose and lipid metabolism, angiogenesis, fibrinolysis, homeostasis and control of vascular tone (Tong H. V. et al., 2017).

Adipose tissue cells are a source of many biologically active substances: adiponectin, leptin, angiotensin, resistin, visfatin, acetylating protein, sex steroids, glucocorticoids, TNF α, IL 6 and free fatty acids, which affect metabolism. Obesity disrupts the balance of pro-inflammatory and anti-inflammatory adipokines, contributing

to the development of many diseases, including metabolic syndrome (Wasim M. et al., 2016).

An increase in the volume of visceral adipose tissue disrupts the secretion of adipokines and leads to the development of chronic low-intensity inflammation, which is mediated by the infiltration of macrophages into adipose tissue (Hemat Jouy S. et al., 2024). The link between inflammation and metabolic syndrome has been confirmed by a number of studies (Eckel R. H., Grundy S. M. & Zimmet P. Z., 2005; Monteiro R. & Azevedo I., 2010), as is the link between an increase in visceral fat mass and the development of metabolic syndrome (Després J. P. & Lemieux I., 2006).

Current research indicates that visceral adipose tissue functions as a paracrine and endocrine organ, secreting a number of adipokines, some of which have pro-inflammatory and atherogenic effects: leptin, tumour necrosis factor α (TNF α), resistin, interleukin 6 (IL 6), fatty acid binding protein, while others have anti-inflammatory and protective properties — adiponectin (Khan M. & Joseph F., 2014).

Adiponectin is a hormone, a polypeptide consisting of 244 amino acids, synthesized and secreted by white adipose tissue, mainly adipocytes (Liu Y. et al., 2015; Qiao L. et al., 2012).

It is one of the most studied adipokines to date. First described in the mid-1990s, analysis of its regulation and physiological effects has proven to be extremely important and has complemented the understanding of the mechanisms involved in systemic metabolic homeostasis (Wang B. et al., 2018).

The main functions of adiponectin are classified as insulin-sensitising, anti-fibrotic (found in many tissues, especially the kidneys, liver and adipose tissue), anti-apoptotic and anti-inflammatory, and it also positively modulates the endocrine system (Nguyen T. M. D., 2020). At the systemic level, adiponectin is capable of regenerating tissues (Zhang L. et al., 2019).

This hormone exists in the body in various forms, such as monomers, trimers, and hexamers. It acts through its receptors, adipoR1 and adipoR2, to influence multiple metabolic processes. AdipoR1 activation mainly promotes mitochondrial biogenesis and glucose uptake through AMPK (adenosine monophosphate-dependent kinase) and p38MAPK pathways. AdipoR2 activation is involved in fatty acid oxidation via the PPARα pathway and provides cytoprotective and anti-inflammatory effects through NF κB modulation. Together, these pathways contribute to the regulation of energy metabolism and inflammatory responses in various tissues, including muscle, liver, kidney, brain, and bone, and increase insulin sensitivity (Krause M. P. et al., 2008). Weight loss increases the level of adiponectin in the body. A decrease in adiponectin is primarily associated with insulin resistance, dyslipidaemia, and the development of laminitis and atherosclerosis (Yadav A. et al., 2013).

The next major adipokine is leptin. It should be noted that leptin and adiponectin have opposite effects on inflammation and insulin resistance.

Leptin is a peptide hormone consisting of 167 amino acids that regulates energy metabolism and is mainly produced by fat cells and enterocytes in the small intestine (Wannamethee S. G. et al., 2007). Leptin was discovered in 1994 as a product of the OB gene in laboratory mice.

The hormone is responsible for regulating metabolic, neuroendocrine and energy processes in the body.

It is considered an independent risk factor for cardiovascular disease (CVD) and a key link between obesity and increased cardiovascular risk (Wannamethee S. G. et al., 2007; Reilly M. P. et al., 2004).

Leptin may also play a role in the immune response by stimulating the proliferation of T helper cells and the production of pro-inflammatory cytokines such as IL 6, which in turn stimulates the synthesis of C-reactive protein (CRP) in the liver. In addition, leptin produced by adipocytes can directly induce IL-6 production, leading to a further increase in CRP synthesis in the liver (Kamei N. et al., 2006).

In horses, leptin concentration increases proportionally to adipose tissue mass, making it a critical biomarker and potential mediator in equine metabolic syndrome (Buff P. R. et al., 2002).

Leptin also interacts closely with insulin metabolism. This hormone increases insulin sensitivity, promoting glucose regulation in the liver and lipid oxidation (Esteghamati A. et al., 2009). However, the literature shows that insulin-resistant horses have elevated blood leptin concentrations, indicating their possible resistance to leptin (Zhao S. et al., 2020).

In addition, leptin receptors have been detected in the lamellar tissue of horses, and hyperleptinaemia is thought to contribute to endothelial dysfunction, oxidative stress and pro-inflammatory conditions in the lamellae, potentially exacerbating laminitis pathology (Correia M. L. & Rahmouni K., 2006).

Based on this, an increase in fat mass results in impaired regulation of adipokines, including leptin and adiponectin, as well as inflammatory mediators, which can affect glycaemic control, inflammation and cardiovascular function (Radin M. J., Sharkey L. C. & Holycross B. J., 2009).

Thus, the determination of leptin and adiponectin in horses are objective, biologically significant indicators of obesity and metabolic health. Their integration with clinical assessment and insulin diagnostics improves the identification of animals with metabolic disorders and directs treatment strategies towards reducing morbidity.

Future research should focus on determining breed- and season-specific reference values for leptin and adiponectin and elucidating their epigenetic modulation to improve the management of equine metabolic health.

Objective. To evaluate the levels of adipocytokines (adiponectin and leptin), their ratio and correlation with the development of obesity in horses.

Materials and methods. The study examined horses, mainly of the Ukrainian riding breed, kept in state research farms in the Poltava region. The animals were divided into two groups: 9 clinically healthy horses and 9 horses diagnosed with obesity, with a total of 18 animals examined. Experimental studies were conducted at the National Scientific Centre ‘Institute of Experimental and Clinical Veterinary Medicine’.

The feeding and housing conditions met the physiological needs of the animals: the diet was balanced in terms of the main nutritional components, the animals had constant access to water and the opportunity for active grazing. All animals underwent a general clinical examination in accordance with standard procedures. The physical condition and body condition scoring (BCS) were assessed by two independent veterinary experts. Blood was collected from the jugular vein on an empty stomach into 10 ml Vacuette vacuum tubes for further serum extraction in accordance with biochemical testing methods.

Glucose levels were determined using the hexokinase test, in which glucose was oxidised to glucose 6 phosphate, and the resulting NADH was determined spectrophotometrically. Electrochemiluminescence immunoassay (ECLIA) was used for insulin analysis.

The calculation of integral indices, which are relevant in the study of insulin resistance, was performed according to the literature data (Melnik A. A. et al., 2024; Gutch M. et al., 2015).

Adiponectin levels were determined by ELISA using the EA2500 1, Human Adiponectin ELISA kit; leptin levels were determined by ELISA using the Human Leptin (LEP) ELISA Kit (Cloud-Clone Corp., USA). The ELISA was performed, the reaction was recorded, and the results were interpreted in accordance with the instructions of the test system manufacturers and using the Stat Fax 4700 immunoenzymatic analyser.

When conducting the experimental studies described in this paper, all manipulations with the horses involved in the studies were carried out in accordance with the basic principles of bioethics, in accordance with Article 26 of the Law of Ukraine 'On the Protection of Animals from Cruel Treatment', the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (1986) and the 'General Ethical Principles for Animal Experiments' adopted by the First National Congress on Bioethics (2012).

Statistical analysis of the data was performed using Minitab 19, Minitab Inc, in a free trial version. Based on the results of statistical processing, the tables show non-parametric indicators such as: mean value (M) and arithmetic mean error (m); a significant difference between groups was established based on the Mann Whitney criterion ($p < 0.05$).

Results. Based on the results of the studies, the relationship and level of influence of adipokines, in particular adiponectin and leptin, and carbohydrate metabolism in horses with normal weight and obese horses were studied (Table).

Table

Biochemical blood parameters in horses (M ± m; n = 9)

Indicators	Clinically healthy horses	Obese horses
Leptin, ng/ml	4,24 ± 0,16	16,42 ± 0,40*
Adiponectin, ng/ml	16,81 ± 0,22	6,32 ± 0,14*
Leptin/adiponectin ratio (LAR)	0,25 ± 0,011	2,65 ± 0,08**
Glucose, mmol/L	4,81 ± 0,41	7,52 ± 0,62**
Insulin, mU/ml	16,21 ± 2,12	38,88 ± 4,05*
HOMA-IR index	3,0 ± 0,15	9,6 ± 0,34**
HOMA-β index	88,5 ± 0,48	73,8 ± 0,52**

*Note: * — $p \leq 0,05$; ** — $p \leq 0,01$.*

A comparative analysis of metabolic indicators in clinically healthy horses and obese animals revealed significant differences, indicating the development of insulin resistance and metabolic imbalance in horses with excessive body weight.

In the group of obese horses, a significant increase in leptin levels was observed, 3.9 times higher ($p < 0.05$) compared to healthy animals. Since leptin is involved in the regulation of energy homeostasis and transmits signals to the brain about fat reserves in the body, an increase in its level indicates a disruption of this function (Zhou Y. & Rui L., 2013). In conditions of obesity, the transmission of the hormonal signal from leptin to the receptor in the hypothalamus is disrupted, leading to impaired leptin transport.

Adipocytes receive information that leptin is not working and begin to synthesise new portions of it (Wang Y. et al., 2014), which provokes the development of leptin resistance.

It should be noted that leptin resistance is not uniform: the concept of selective leptin resistance explains that some actions of leptin, such as sympathetic activation, which contributes to cardiovascular effects, may persist even when metabolic satiety signalling is impaired. This selective resistance may partially explain the higher cardiovascular and laminitis risks in horses compared to metabolically healthy obese horses (Mark A. L. et al., 2002; Correia M. L. & Rahmouni K., 2006).

In turn, leptin resistance also plays an important role in the development of insulin resistance (Zhou Y. & Rui L., 2013). Leptin promotes insulin secretion and increases the sensitivity of peripheral tissue receptors to insulin, which increases glucose utilisation. This fact is reflected in studies that have shown that leptin levels were significantly higher in patients with diabetes mellitus and metabolic syndrome and had a significant positive correlation with plasma insulin (Moonishaa T. et al., 2017; Beyazıt F. & Ünsal M. A., 2017). Our data on the direct relationship between the HOMA index, insulin levels and leptin concentration are consistent with these findings.

It should also be noted that the development of leptin resistance, which develops as a result of obesity, provokes the formation of an excessive amount of free radicals, the development of oxidative stress and inflammation (de Git K. C. G. et al., 2018). Numerous studies in horses emphasise the link between leptin and metabolically active fat deposits and the associated risk of disease (Esteghamati A. et al., 2009).

At the same time, the level of adiponectin was significantly lower by 2.7 times ($p < 0.05$) compared to healthy animals and had a negative correlation with the HOMA index. Calculation of the HOMA IR index showed its significant increase in the obese group by 3.2 times ($p < 0.01$), which is consistent with the literature data on the presence of insulin resistance in animals with excessive body weight. The HOMA β index, which reflects the functional activity of pancreatic β cells, was moderately reduced in obese horses by 1.2 times, indicating compensatory changes in β cell function and mass in response to increased insulin demand.

According to the literature, this fact is associated with an increased risk of developing atherosclerosis, myocardial infarction, diabetes mellitus, metabolic syndrome and obesity (Gairolla J. et al., 2017; Kang Y. et al., 2013).

Other studies indicate a correlation between adiponectin levels and insulin levels and adipose tissue mass (Gauff F., Patan-Zugaj B. & Licka T. F., 2013).

Current literature indicates that if serum adiponectin levels are low in the body, pro-inflammatory cytokine levels are elevated (Cornier M. A. et al., 2008). This imbalance in the inflammatory state leads to endothelial cell dysfunction, contributing to the loss of their vasodilatory, antithrombotic and antiatherogenic properties (Frühbeck G. et al., 2017), which is probably a very common biological response. Adiponectin has also been shown to reduce the expression of adhesion molecules in endothelial cells, inhibit the proliferation of vascular smooth muscle cells, inhibits the differentiation of monocytes into macrophages, the formation of foam cells and the secretion of TNF α by macrophages, promotes the differentiation of preadipocytes into mature adipocytes, and its deficiency negatively affects the development of these functions (Tian F. et al., 2010).

Discussion. Thus, our results indicate that obesity is accompanied by an imbalance of adipokines, which is reflected in the literature (Rasouli N. & Kern P. A., 2008).

The main marker of the pathophysiological function of both adipokines, which indicates an imbalance between anti-inflammatory and pro-inflammatory states and

adipose tissue dysfunction, is the leptin/adiponectin ratio (LAR) (Frühbeck G. et al., 2018).

Under normal conditions, the ratio of leptin to adiponectin is 1:2, which means a LAR value of 0.5; thus, higher values are associated with an increase in cardiovascular risk, metabolic risk, and insulin resistance (Han S. K. et al., 2024). Our research showed that the leptin/adiponectin ratio (LAR) was particularly informative, exceeding the similar indicator in clinically healthy horses by more than 10 times in obese animals (2.6 ± 0.08 vs. 0.25 ± 0.011, $p < 0.01$), indicating adipose tissue dysfunction and the development of related pathologies. These results show that LAR may be a useful index for insulin resistance in clinical practice and a good indicator for assessing the effectiveness of antidiabetic therapy. Indeed, it has been reported that both the calculated HOMA IR index and LAR can be used to determine insulin resistance (Rueda-Clausen C. F. et al., 2010; Oda N. et al., 2008).

Biochemical analysis of other indicators, which are primarily assessed when determining insulin resistance and obesity, also showed a significant increase in blood plasma glucose concentration in obese horses by 56.7% ($p < 0.01$), indicating a disturbance in carbohydrate metabolism. In response to the increase in glucose levels, a 2.4-fold increase in insulin levels was observed ($p < 0.05$), indicating a compensatory response of the body to reduced tissue sensitivity to insulin and consistent with data on increased leptin levels and decreased adiponectin (Marycz K. et al., 2018).

The results obtained are consistent with current understanding of the pathogenesis of metabolic syndrome in animals and confirm that obesity in horses is accompanied by complex disorders of hormonal and carbohydrate regulation, requiring early diagnosis and correction.

Conclusions. Glucose concentration, insulin level, and the HOMA IR and HOMA β indices calculated on their basis remain the most important markers of insulin resistance in horses, as together they allow the pathogenesis of this condition to be identified, assessed, monitored, and supplemented.

In summary, serum leptin, adiponectin, and LAR can be used as an integrated marker of obesity, insulin resistance, and vascular dysfunction and are an integral part of the pathophysiology of these conditions, making them useful for accurate diagnosis and treatment guidance.

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