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Metabolism of vitamin D, Calcium and Phosphorus and their disorders in goats

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The review article presents materials on the metabolism of the most common vitamins of group D ergocalciferol (D_2), cholecalciferol (D_3), as well as essential macronutrients Ca and Phosphorus and their disorders in goats. Since the primary forms of vitamin D (D_2 and D_3) are biologically inactive and must undergo several stages of hydroxylation to be activated, the biological role and importance for the body of active metabolites of vitamin D_3 25OH D_3 (synthesised mainly in the liver under the influence of hepatic cytochromes P450) and 1, 25$(OH)_2$ D_3 and 24,25$(OH)_2$ D_3 (their synthesis occurs via 1α-hydroxylase in the mitochondria of proximal cells of the convoluted tubules of the kidneys).

It is believed that the liver, while playing an important role in the metabolism of vitamin D and its metabolites and producing 25OH D_3, is also the only organ that synthesises DBP, which transports 25OH D_3 to tissues and maintains its concentration in the circulatory system.

Vitamin D becomes biologically active only after the second stage of hydroxylation is completed. Renal 1α-hydroxylase (CYP27B1), regulated by parathyroid hormone (PTH), plays an important role in the transformation of the extracellular substrate 25OH D_3 to 1,25$(OH)_2$ D_3, which exerts its effect on target cells and tissues by binding to the nuclear vitamin D receptor. Alternatively, 1,25$(OH)_2$ D_3 can bind to the plasma membrane VDR and induce non-genomic actions, in particular, stimulation of intestinal calcium transport.

Vitamin D is a steroid substance that is essential for all vertebrates to maintain calcium and phosphorus metabolism within optimal limits, a healthy skeleton, muscle contraction, modulation of cell growth and neuromuscular function. Calciferol also regulates the immune system, inhibits the development of pathological cells, angiogenesis and inflammatory reactions. The active form of vitamin D, 1,25$(OH)_2$ D_3, stimulates intestinal absorption and renal Ca reabsorption and maintains its minimum physiological level in the blood.

Vitamin D deficiency in goats leads to a decrease in productivity, causes a decrease in intestinal and renal calcium reabsorption, which leads to the increase in parathyroid hormone levels. This process leads to activation of osteocytes and, as a result, accelerates bone demineralisation, causing the development of many diseases in adults, including nutritional and fibrous osteodystrophy, secondary osteodystrophy, endocrine dysfunction), as well as rickets in young animals. The development of non-skeletal pathologies, in particular, inflammatory, neoplastic and autoimmune diseases, is also associated with cholecalciferol deficiency in the body. In addition, disorders of D-vitamin and calcium-phosphorus metabolism in goats cause the development of postpartum hypocalcaemia and postpartum hypophosphatemia.

In the animal body, calcium and phosphorus homeostasis is maintained by a coordinated interaction of absorption and reabsorption through the gastrointestinal tract and kidneys, as well as by storage and

mobilization from bone tissue and is regulated mainly by biologically active cholecalciferol metabolites - 25OH D_3, 1,25$(OH)_2$ D_3, as well as parathyroid hormone (PTH; synthesised by the pineal glands) and calcitonin (CT; produced by sparafollicular (light) thyroid C cells) and fibroblast growth factor-23 (FGF23).

In contrast to monogastric animals, small ruminants do not modulate renal calcium excretion in response to calcium limitation in the diet. The mobilization of Ca and P from the skeleton is stimulated by PTH through osteoclast activation mediated by receptor activator of nuclear factor-κB (RANK). Vitamin D maintains Ca (by stimulating CaZB) and P homeostasis (the direct rapid action of 1,25$(OH)_2$ D_3 has been proven to have a direct effect on the absorption of these vital elements in the intestine, reabsorption of these cations in the renal tubules and their mobilization from bone tissue).

Phosphorus is a component of adenosine triphosphate (ATP) and nucleotides. Macroergic phosphate compounds, among which the main one is adenosine triphosphate acid, provide both the accumulation of energy reserves and its consumption (ATP, ADP, creatine phosphate), affecting protein, lipid, carbohydrate, mineral, and energy metabolism. An interaction between vitamin D and fibroblast growth factor 23 (FGF23), a bone hormone that causes the development of phosphaturia and reduces the synthesis of 1,25$(OH)_2$ D_3, has been identified.

Despite the multidirectionality of etiological factors, common to all forms of osteodystrophy is a disruption of the processes of bone formation and renewal, which is manifested by increased mobilization of calcium, phosphorus and other elements from bone tissue, so the pathology is accompanied by osteomalacia, osteoporosis and osteofibrosis, and a violation of the mechanism of maintaining their homeostasis.

The main factors of osteodystrophy in animals are feeding disorders and physical inactivity, and the leading links in its pathogenesis are the imbalance between bone formation and resorption.

The main methods for diagnosing disorders of D-vitamin and calcium-phosphorus metabolism in goats are clinical, physical, biochemical, enzyme-linked immunosorbent assays and pathological and morphological studies. Biochemical analysis in goat serum determines the content of total calcium, inorganic phosphorus, activity of alkaline phosphatase and its isozymes, and immunoassay the concentration of 25OH D_3, 1,25$(OH)_2$ D_3, calcitonin and parathyroid hormone.

Keywords: goats, vitamin D, metabolites, metabolism, calcium, phosphorus, liver, kidneys.

Problem statement and analysis of recent research. Over the past decade, the number of scientific publications on the biological role of vitamin D, methods of diagnosis, treatment and prevention of D-vitamin metabolism disorders in animals has increased significantly [1]. New knowledge about the biological and clinical importance of the steroid hormone 1,25-dihydroxyvitamin D_3, 1,25$(OH)_2$ D_3, and its vitamin D receptor (VDR) has made a significant contribution to bone strengthening. At the same time, various diseases associated with vitamin D deficiency in goats have been reported worldwide. Cholecalciferol deficiency is an important animal health problem that can cause a decrease in bone density and lead to osteoporosis and fractures [2–3].

The main physiological role of vitamin D is thought to be in the development and maintenance of skeletal health. Almost a century ago, it was proven that vitamin D deficiency is the cause of rickets in goats, but over the past few decades, numerous studies have linked vitamin D deficiency to the development of a wide range of non-skeletal pathologies, including inflammatory, neoplastic and autoimmune diseases [4–5]. Calciferol also regulates the immune system, suppresses the development of pathological cells, angiogenesis and inflammatory reactions [6]. The active form of vitamin D, 1,25$(OH)_2$ D_3, is necessary to stimulate intestinal absorption and renal reabsorption of Ca, as well as to maintain its minimum physiological level in the blood. A significant decrease in vitamin D during pregnancy in goats leads to impaired calcium metabolism and the development of hypocalcaemia [7].

The most common macronutrient in the body of animals is Ca^{2+}. About 99% of calcium in the

body performs structural functions as a component of bones and teeth, and only about 1% is found in tissues and extracellular fluids. Calcium is crucial for the regulation of various processes in the body, including blood clotting, muscle contraction, cell signalling, membrane permeability, enzyme stabilisation, and hormone activation and release [8]. In goat blood plasma, the total calcium content ranges from 2,0 to 3,0 mmol/l, and calcium deficiency can lead to growth and developmental delays and pathological risks, including osteoporosis, rickets, osteochondrosis and hypocalcaemia in goats [7, 9, 10].

Phosphorus is an important macronutrient with a wide range of vital biological functions. Phosphorus plays a structural role at the tissue, cellular and molecular levels of any living organism. The integrity of the cell depends on phosphorus, which is an integral part of phospholipids that form cell membranes. Phosphorus is also a component of DNA and RNA molecules. Hypophosphatemia in goats can lead to a number of clinical signs and conditions, loss of appetite, anorexia, impaired growth and reproductive function, muscle weakness, intravascular hemolysis; bone fractures are common, as well as rickets in young animals and osteomalacia in adults [11–12].

The purpose of the research is to analyse a wide range of international and domestic scientific publications on the metabolism of vitamin D, its active metabolites, as well as essential macronutrients calcium and phosphorus and their disorders in goats.

Material and methods of the study. Data collection, analysis, and synthesis of the systematic review were performed in accordance with the PRISMA guidelines for writing systematic reviews [13].

The English language sources were searched in the Web of Science Core Collection (apps.webofknowledge.com), the Europe Pub Med Central database (europepms.org/), and the domestic sources were searched in the Scientific Periodicals of Ukraine database (www. irbis-nbuv.gov.ua/cgi-bimn/irbis_nbuv/cgiirbis_64.exe).

At the first stage of the search, we used the search and filtering tools of scientometric databases of scientific literature.

The keywords used for the search were: goats, vitamin D, metabolites, metabolism, calcium, phosphorus, liver, kidneys. For each search query, refinement filters were applied in accordance with the purpose of the search criteria, articles published in the period 2010-2023. The studies were conducted in the EU and Ukraine and belonged to the category of veterinary medicine. The sources that remained after the refinement filters were examined by the authors in two stages. At the first stage, they studied the abstracts and selected studies that met the questions and criteria of the systematic review. At the second stage, the selected articles were studied in detail, and the data were systematised and analysed.

Results and discussion. Biological role of vitamin D. It is known that vitamin D (25OH D_3) plays an important role in the health and diseases of the musculoskeletal system of animals, and its deficiency is widespread in the world [14–15]. The study of issues related to the impact of varying degrees of supply of goats with fat soluble vitamins, in particular vitamin D, on certain links of their metabolism is in the focus of attention of domestic and foreign researchers [16–18].

Vitamin D is essential for humans and animals, and its deficiency causes rickets in children and osteomalacia in adults. Vitamin D deficiency causes a decrease in intestinal and renal calcium reabsorption, which leads to an increase in parathyroid hormone (PTH) levels. This process causes activation of osteocytes and, as a result, accelerates bone demineralisation [19].

Vitamin D is widely known as an anti rickets factor. It acts as a steroid hormone in maintaining optimal serum calcium and phosphorus levels. These effects are well known and are achieved by enhancing the absorption of the above macronutrients in the intestine, increasing bone resorption and reducing urinary excretion of calcium and phosphorus [20]. Recently, an interaction between vitamin D and fibroblast growth factor 23 (FGF23), a bone hormone that causes the development of phosphaturia and reduces the synthesis of 1,25$(OH)_2$ D_3, has been identified. The main systemic stimuli of FGF23 secretion are an increase in the level of 1,25$(OH)_2$ D_3 and an increase in the intake of phosphorus from feed [21]. According to Al. Mheid I., A.A. Quyyumi [22], FGF23 is associated with vascular dysfunction, ventricular hypertrophy and cardiovascular disease, and it is considered one of the factors responsible for the negative cardiovascular effects of vitamin D deficiency.

Vitamin D, in particular, has other important functions in the body, including the reduction of inflammation, as well as the modulation of cell growth, neuromuscular and immune function, and glucose metabolism. Many genes encoding proteins that regulate cell proliferation, differentiation and apoptosis are partially modulated by

vitamin D. Many tissues have vitamin D receptors, and some convert 25 OH D_3 to 1,25$(OH)_2$ D_3 [23–25].

However, there are still questions about the optimal doses of vitamin D to maintain animal health, as well as recommendations for the daily requirement of vitamin D. The body of goats is supplied with vitamin D in two ways exogenous (from feed of plant and animal origin) and endogenous (synthesis of cholecalciferol in the skin under the influence of ultraviolet irradiation) [26]. According to M. Kohler, F. Leiber et al. [17], the content of vitamin D_3 and its metabolites in the blood serum of Alpine goats is in the range of: a) 25OH D_3 – 130 nmol/l; b) 1,25$(OH)_2$ D_3 – 116,0 pmol/l; c) 25$(OH)_2$ D_2 – 43,5 nmol/l; d) 25$(OH)_2$ D_3 – 103,5 nmol/l, and according to the results of studies by Kovács S., Wilkens M. R. [26], the content of 25(OH)D_3 in goats aged 18–20 weeks was 108,8 nmol/l, and 1,25$(OH)_2$ D_3 – 211,6 pmol/l.

Vitamin D is available to animals from two sources: 1) the isomerisation of 7-dehydrocholesterol (7-DHC) in the skin to vitamin D_3 after exposure to UVB irradiation; 2) the intake of vitamin D_2 or D_3 in the feed. Only some foods, such as cod liver oil and oily fish (salmon and sardines) naturally contain high concentrations of vitamin D_3. Vitamin D_2 is present in some plants due to the conversion of ergosterol to vitamin D_2 under the influence of ultraviolet light. Ultraviolet light in the range of 270 to 315 nm is necessary for the conversion of 7-DHC in the skin to provitamin D_3, which is further thermally isomerised into vitamin D_3 within three days [27].

A number of authors [24–28] point out that the primary forms of vitamin D (D_2 and D_3) are biologically inactive and must undergo several hydroxylation steps to be activated. The primary transformation of calciferol (25-hydroxylation) occurs mainly in the liver. A number of hepatic cytochromes P450 are thought to perform 25-hydroxylation of vitamin D, including CYP27A1, CYP3A4, CYP2R1 and CYP2J3, and this step in vitamin D metabolism is largely unregulated [28]. The liver plays an important role in vitamin metabolism by synthesising bile for the absorption of fat-soluble vitamins (A, D, E, K) [29]. Deficiency of 25 OH D_3 is associated with the development of hypertension, autoimmune diseases, and cancer, and its optimal level is a means of maintaining bone density. Thus, vitamin D can inhibit bone resorption and promote bone mineralisation and regeneration [30–31].

The liver not only produces 25 OH D_3, but is also the only organ that synthesises DBP, which transports 25 OH D_3 to tissues and maintains its concentration in the 25 OH D_3 circulation. The liver is believed to play an important role in the metabolism of vitamin D and its metabolites [32].

The next step in the transformation of vitamin D into biologically active metabolites, 1α-hydroxylation, occurs via 1α-hydroxylase in the mitochondria of proximal renal convoluted tubule cells with the subsequent formation of 1,25$(OH)_2$ D_3 and 24,25$(OH)_2$ D_3. Vitamin D becomes biologically active only after the second stage of hydroxylation is completed [1]. Renal 1α-hydroxylase (CYP27B1), which is regulated by parathyroid hormone (PTH), plays an important role in vitamin D endocrinology. In particular, CYP27B1 plays a role in the transformation of the extracellular substrate 25 OH D_3 to 1,25$(OH)_2$ D_3, which subsequently activates the VDR [33–34]. 1,25$(OH)_2$ D_3 exerts its effect on target cells and tissues by binding to the nuclear vitamin D receptor (VDR) and heterodimerising with the retinoid X receptor (RXR). This complex exerts genomic action as a transcription factor to regulate target genes containing a vitamin D response element in their promoter. Alternatively, 1,25$(OH)_2$ D_3 can bind to the plasma membrane VDR and induce non-genomic effects, in particular, stimulation of intestinal calcium transport [32, 35].

Calcium and phosphorus metabolism. Calcium is actively involved in skeletal mineralisation, muscle contraction, transmission of nerve impulses, blood clotting and hormone secretion [36]. In animals, it is essential for maintaining the nervous system. At neuromuscular synapses, Ca^{2+} ions promote the release of acetylcholine and its binding to the cholinergic receptor, and in the presence of excess acetylcholine, they activate cholinesterase, an enzyme that breaks down acetylcholine. Ca^{2+} ions contained in the sarcoplasmic reticulum promote the interaction of actin and myosin to ensure the contraction of muscle fibres in the presence of magnesium ions. In smooth muscle cells, as well as in the myocardium and cardiac conduction system, calcium ions are directly involved in the generation of nerve impulses [37].

Calcium compounds are found in various forms in the blood. Out of 10–12 mg/100 ml of total plasma calcium, about 4 mg is bound to blood proteins, 5–7 mg is contained in ionised form, and 2–3 mg is in non-ionised form (2,5-3,0, 1,0, 1,25-1,75, and 0,5-0,75 mmol/l, respectively). Ionised calcium is involved in metabolism, activates the reticuloendothelial system, maintains the sympathetic nervous system's tonus, and

reduces the permeability of blood vessels and cell membranes. In addition, this vital macronutrient activates trypsin, promotes the conversion of prothrombin to thrombin, stimulates the phagocytic function of leukocytes, etc. [38].

The calcium content in the blood plasma is regulated by calcitonin, whose activity depends on the physiological state of animals (pregnancy and lactation). For example, postpartum hypocalcaemia occurs as a result of a disturbance in calcium homeostasis in the body [39].

Phosphorus also plays an important role in metabolic processes. It is a part of many metabolic intermediates and, most importantly, is a component of adenosine triphosphate (ATP) and nucleotides. Macroergic phosphate compounds, among which adenosine triphosphate is the main one, are universal energy accumulators and donors, present in all cells of the body and ensure both the accumulation of energy reserves in the body and its consumption (ATP, ADP, creatine phosphate). That is, all types of metabolism: protein, lipid, carbohydrate, mineral, energy, etc. [40].

Phosphorus is one of the main structural elements of the body. All synthesis processes associated with skeletal formation, muscle gain, synthesis of milk components, and hair growth are carried out with the participation of phosphate acid. In particular, phosphorus is part of the structure of nucleic acids, which are carriers of genetic information and regulate protein biosynthesis and immunity. Phosphoric acid salts are involved in the construction of buffer systems in the skin [41].

It has been established that vitamin D maintains the homeostasis of Ca (by stimulating CaZB) and P (the direct rapid action of $1,25(OH)_2 D_3$ has been proven), realising itself through direct influence on the absorption of these vital elements in the intestine, reabsorption of these cations in the renal tubules and their mobilisation from bone tissue [33].

According to Oriana M. Köhler and Walter Grünberg [42], calcium and phosphorus homeostasis is maintained by a coordinated interaction of absorption and reabsorption through the gastrointestinal tract and kidneys, as well as by storage and mobilisation from bone tissue, and is regulated primarily by parathyroid hormone (PTH), 1,25 dihydroxycholecalciferol ($1,25(OH)_2 D_3$) and calcitonin (CT) and fibroblast growth factor 23 (FGF23). The release of PTH from the pituitary gland is controlled by the concentration of ionised calcium in the blood plasma, mediated by the Ca^{2+}-sensing receptor (CaSR). Within minutes, a decrease in blood Ca^{2+} causes the release of PTH from the pituitary gland, which stimulates the mobilisation of Ca and P from the skeleton [12, 43, 44]. In the kidneys, PTH stimulates the expression and activity of 1α-hydroxylase (CYP27B1), an enzyme key to the synthesis of $1,25(OH)_2 D_3$ [45].

In contrast to monogastric animals, small ruminants do not modulate renal calcium excretion in response to calcium restriction in the diet. It has been shown that goats have a greater ability to compensate for calcium homeostasis problems than sheep [46]. Abdullah Ben-awadh et al. [47] found that the mobilisation of Ca and P from the skeleton is stimulated by PTH through osteoclast activation mediated by receptor activator of nuclear factor-κB (RANK) [48].

Disorders of D-vitamin and calcium-phosphorus metabolism in goats. Vitamin D is an essential vitamin for humans and animals, and vitamin D deficiency in goats causes significant economic losses to owners due to the development of nutritional osteodystrophy, fibrous osteodystrophy, secondary osteodystrophy and rickets, which leads to reduced productivity and the development of various metabolic diseases, especially in young animals. The most common disorders of calcium and phosphorus metabolism are nutritional osteodystrophy, postpartum hypocalcaemia, and postpartum hypophosphaemia [49].

Alimentary osteodystrophy is a chronic disease that occurs with impaired phosphorus and calcium metabolism and is characterised by systemic bone dystrophy due to insufficient intake of calcium, phosphorus, energy, protein, and vitamin D from the diet [50].

In addition to nutritional osteodystrophy, secondary osteodystrophy is diagnosed as a consequence of other diseases (ketosis, liver disease, endocrine dysfunction) and enzootic osteodystrophy, which occurs due to an imbalance of macro- and microelements (recorded in endemic areas depleted in cobalt, zinc, copper, manganese). Despite the diversity of etiological factors, all forms of osteodystrophy are characterised by impaired bone formation and renewal, which is manifested by increased mobilisation of calcium, phosphorus and other elements from bone tissue. Mineral losses are not compensated for in a timely manner. They are accompanied not only by osteomalacia, but also by osteoporosis and osteofibrosis, and disruption of the mechanism of maintaining calcium and phosphorus homeostasis. A decrease

in calcium concentration in the blood and tissues results in a decrease in skeletal and smooth muscle tone, muscle cramps, hypotension and atony of the fore stomach. The animals' taste is distorted, the skeleton becomes thinner, the thorax is deformed, and lying down occurs [51].

A number of authors have reported that the $25(OH)D_3$ content is significantly affected by skin pigmentation in sheep and goats [52–54]. It has been demonstrated that heavy fleece and pigmented skin reduce the biosynthesis of vitamin D in the skin compared to sheared sheep with light pigmentation [55].

The main factors of osteodystrophy in animals are feeding disorders and physical inactivity, and the leading links in its pathogenesis are the imbalance between bone formation and resorption. The role of the nutritional factor is played by unbalanced and insufficient feeding of animals. Of particular importance is the insufficient intake of calcium and phosphorus in the feed and the disturbance of the ratio of these elements in the diet, as well as vitamin D. There are clinical, histological, physical and biochemical methods for diagnosing osteodystrophy. Physical examinations (dual-energy X-ray absorptiometry and computed tomography) require expensive special sophisticated equipment [56].

According to Yu. Maslak [51], among the clinical signs of more severe osteodystrophy in goats were tuberosity and partial lysis of the last pairs of ribs, shakiness of incisor teeth, and liver tenderness during palpation. The level of total calcium in goats with clinical signs of the disease was in the range of 2,58–3,08 mmol/l (optimal – 2,3–3,0 mmol/l), phosphorus – 1,15–1,34 mmol/l (1,6–2,6 mmol/l), Ca:P ratio, respectively –1,98–2,49; an increase in the activity of ALP and its bone isoenzyme was observed. Among the connective tissue biopolymers, there were high levels of CHT, GAG and their fractions, which is explained by the involvement of not only bones but also liver and intervertebral discs in the pathological process of connective tissue.

According to the results of a study by Paulo Bandarra, Saulo Pavarini et al. in goats [57], the symptoms of osteodystrophy were characterised by an increase in the upper and lower jaws, shaky incisors, tongue protrusion, shortness of breath, and chewing disorders in goats. In the blood serum, the calcium content was in the range of 0,99-2,92 mmol/l, phosphorus 1,27-2,16 mmol/l, alkaline phosphatase activity – 387 U/l (normal - up to 85 U/l). Microscopically, intensive proliferation of loose connective tissue around the bone trabeculae was observed, many of which were partially or completely demineralised.

According to Y. Maslak, O. Mitrofanov, A. Sobakar [58], clinical signs of osteodystrophy in goats were characterised by thinning and humping of the ribs, and loose incisor teeth. In some goats, partial lysis of the last pair of ribs was observed. The biochemical parameters of the blood serum of goats with clinical signs of osteodystrophy were as follows: ALT activity – 28,5±1,04 U/l, ACAT – 38,9±1,56 U/l, total calcium 2,8±0,05 mmol/l, inorganic phosphorus 1,2±0,02 mmol/l, chondroitin sulfate 0,24±0,04 g/l.

Rickets is a metabolic bone disease of young animals due to a deficiency of calcium, phosphorus, and vitamin D in the diet. The pathogenesis of rickets lies in the impaired mineralisation of the physis and epiphyseal cartilage during endochondral ossification and newly formed osteoid [27, 59]. The pathological picture of rickets is based on primary bone growth retardation with impaired metabolism of vitamin D, calcium, phosphorus and lagging of the mineralisation process from the physiological needs of the body [60].

According to the results of the Mona. S. Zaki [61], goats under 8 months of age were diagnosed with rickets with pronounced clinical signs: anorexia, growth retardation, scoliosis, joint enlargement and curvature of the thoracic limbs. A biochemical analysis of blood serum revealed hyperphosphatemia, hypocalcaemia, and decreased alkaline phosphatase activity against a background of a significant increase in cortisol concentration.

Sharma D. K., Sonawane G. G. [62] described the clinical signs of lambs with rickets: curvature of the thoracic limbs, joint swelling, stiff gait, lameness, and growth retardation. Among the biochemical changes in the blood serum, an increase in the level of alkaline phosphatase (458,10 ± 27,98 U/l), hypocalcaemia (2,28 ± 0,10 mmol/l), and hypophosphatemia (1,34 ± 0,08 mmol/l) were diagnosed. For the treatment of lambs, the CFS-II feed additive was used, which contains vitamins A, D_3, E, nicotinamide, minerals – calcium, manganese, iron, copper and cobalt. According to the results of the tests on the 45th day after the use of the CFS-II feed additive, the affected animals did not show any clinical symptoms of rickets and were in satisfactory condition.

Thompson K., K. Dittmer, H. Blair [63] reported the development of syndromes in lambs characterised by growth retardation, limb defor-

mities and lordosis. Affected lambs appeared normal at birth, but clinical signs usually appeared at 2 months of age and progressed. Initially, the animals were stunted, and with the progression of the disease, they were more laid back.

Lambs with rickets had significantly lower average serum concentrations of calcium and inorganic phosphorus. The activity of total ALP was significantly increased in affected animals. There was no significant difference between affected lambs and control lambs in the mean concentration of 25-hydroxyvitamin D in the blood serum, but the diseased animals had higher concentrations of 1,25-dihydroxyvitamin D [63].

Metabolic bone diseases are relatively common in goats and include osteomalacia and fibrous osteodystrophy. Osteoporosis can result from calcium and phosphorus deficiencies or chronic debilitating diseases, such as gastrointestinal diseases. The vertebrae, skull bones, shoulder blade, and ilium are most often affected and prone to fractures.

According to the results of the study by U. Braun, S. Ohlerth, A. Liesegang [64], goats aged 3–6 years were diagnosed with osteoporosis: curved back, lameness, lying down, general depression, weight loss and reduced milk production. On radiographs, the decrease in mineralisation was most noticeable in the vertebrae and pelvic bones. In one goat, the ribs were soft and flexible, which is characteristic of osteoporosis. All goats had severe hypophosphatemia with inorganic phosphorus concentration of 0,18–0,86 mmol/l, hypomagnesemia (0,80 to 0,87 mmol/l), hypocalcaemia (2,08–2,2 mmol/l), total liver function test was within normal limits, and creatine kinase was elevated (518–1721 U/l, with a normal range of 86-206 U/l).

The main methods of diagnosis of disorders of D-vitamin and calcium-phosphorus metabolism in goats are clinical, physical, biochemical, enzyme-linked immunosorbent and pathological morphological methods of research. Many authors have highlighted the most common clinical signs in sick goats, such as: tuberosity and partial lysis of the last pairs of ribs, loose incisor teeth, liver tenderness during palpation, enlargement of the upper and lower jaws, tongue protrusion, shortness of breath, and chewing disorders. In rickets, curvature of the thoracic limbs, joint swelling, stiff gait, lameness, growth retardation and lordosis.

During the biochemical examination of goat blood, it is important to determine total calcium, inorganic phosphorus, alkaline phosphatase activity and its isozymes in the blood serum, and in the enzyme-linked immunosorbent assay – 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol, calcitonin and parathyroid hormone.

Conclusions. 1. The materials for the review article were collected, analysed, and a systematic review was prepared in accordance with the PRISMA guidelines for writing systematic reviews.The search for English language sources was conducted in the Web of Science Core Collection, the Europe Pub Med Central database of scientific articles, and the search for domestic sources was conducted in the Scientific Periodicals of Ukraine database.

2. The article presents materials on the metabolism of D vitamins: ergocalciferol (D_2), cholecalciferol (D_3), as well as essential macronutrients Calcium and Phosphorus and their disorders in goats. The primary forms of vitamin D (D_2 and D_3) are biologically inactive and must undergo several hydroxylation steps in the liver and kidneys to become active. The first biologically active metabolite of vitamin D_3, 25OH D_3, is synthesised mainly in the liver under the influence of hepatic cytochromes P450, while the other two metabolites, 1,25$(OH)_2$ D_3 and 24,25$(OH)_2$ D_3, are synthesised in the mitochondria of the proximal cells of the renal convoluted tubules by 1α-hydroxylase. The liver is also the only organ that synthesises DBP, which transports 25OH D_3 to the tissues and maintains its concentration in the circulation.

3. Vitamin D is a steroid substance that is essential for all vertebrates to maintain calcium and phosphorus metabolism within optimal limits, a healthy skeleton, muscle contraction, modulation of cell growth and neuromuscular function. Calciferol also regulates the immune system, inhibits the development of pathological cells, angiogenesis and inflammatory reactions. One of the active forms of vitamin D, 1,25$(OH)_2$ D_3, stimulates intestinal absorption and renal reabsorption of Ca and maintains its minimum physiological level in the blood.

4. Calcium and phosphorus homeostasis in animals is maintained by the coordinated interaction of absorption and reabsorption through the gastrointestinal tract and kidneys, as well as by storage and mobilisation from bone tissue, and is regulated mainly by the biologically active metabolites of cholecalciferol – 25OH D_3, 1,25$(OH)_2$ D_3, as well as parathyroid hormone, calcitonin and fibroblast growth factor-23 (FGF23).

5. Vitamin D supports Ca (through stimulation of CaZB) and P homeostasis (proven direct

fast action of 1,25$(OH)_2$ D_3 through direct influence on the absorption of these vital elements in the intestine, reabsorption of these cations in the renal tubules and their mobilisation from bone tissue).

6. Phosphorus is a component of adenosine triphosphate (ATP) and nucleotides. Macroergic phosphate compounds, among which adenosine triphosphate is the main one, ensure both the accumulation of energy reserves and its consumption (ATP, ADP, creatine phosphate), affecting protein, lipid, carbohydrate, mineral, and energy metabolism.

7. Vitamin D deficiency in goats causes a decrease in intestinal and renal calcium reabsorption, which leads to an increase in parathyroid hormone levels. This process causes activation of osteocytes and, as a result, accelerates bone demineralisation, causing the development of many diseases in adult animals, including nutritional and fibrous osteodystrophy, secondary osteodystrophy, postpartum hypocalcaemia and postpartum hypophosphataemia, rickets in young animals, and endocrine dysfunction.

8. Common to all forms of osteodystrophy is a disruption of bone formation and renewal, which is manifested by increased mobilisation of calcium, phosphorus and other elements from bone tissue. The pathology is accompanied by osteomalacia, osteoporosis and osteofibrosis, and disruption of the mechanism of maintaining their homeostasis. The main factors of osteodystrophy in animals are feeding disorders and physical inactivity, and the leading links in its pathogenesis are the imbalance between bone formation and resorption.

9. Clinical and special studies (physical, biochemical, immunoassay and pathological and morphological studies) are informative methods for diagnosing disorders of D-vitamin and calcium-phosphorus metabolism in goats. Biochemical analysis of goat serum determines the content of total calcium and its isoenzymes, inorganic phosphorus, alkaline phosphatase activity and its isoenzymes, and immunoassay - the concentration of 25OH D_3, 1,25$(OH)_2$ D_3, calcitonin and parathyroid hormone.

Information about the conflict of interest. The authors of the article "Metabolism of vitamin D, calcium and phosphorus and their disorders in goats" V.V. Sakhniuk and M.M. Gotsulyak declare that there is no conflict of interest in relation to their contribution and the results of the study. The materials of the article can be published.

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Метаболізм вітаміну D, Кальцію і Фосфору та їх порушення у кіз

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В оглядовій науковій статті викладено матеріали щодо метаболізму найбільш розповсюджених вітамінів групи D – ергокальциферолу (D_2), холекальциферолу (D_3), а також есенціальних макроелементів Кальцію і Фосфору та їх порушень у кіз. Оскільки первинні форми вітаміну D (D_2 і D_3) є біологічно неактивними і для активації мають пройти кілька етапів гідроксилювання, висвітлено біологічне значення для організму активних метаболітів вітаміну D_3 – 25OH D_3 (синтезується переважно в печінці під дією печінкових цитохромів Р450) та 1,25$(OH)_2 D_3$ і 24,25$(OH)_2 D_3$ (їх синтез відбувається в мітохондріях проксимальних клітин звивистих канальців нирок за допомогою 1α-гідроксилази).

Вважається, що печінка, відіграючи важливу роль в обміні вітаміну D та його метаболітів і продукуючи 25OH D_3, є також єдиним органом, що синтезує DBP, який транспортує 25OH D_3 до тканин і зберігає його концентрацію в системі кровообігу.

Вітамін D стає біологічно активним лише після завершення другого етапу гідроксилювання. Ниркова 1α-гідроксилаза (CYP27B1), що регулюється паратгормоном (ПТГ), має важливе значення у трансформації позаклітинного субстрату 25OH D_3 до 1,25 $(OH)_2 D_3$, який здійснює свою дію на клітини-мішені і тканини через зв'язування з ядерним рецептором вітаміну D. Альтернативно 1,25$(OH)_2$ D_3 може зв'язуватися з VDR плазматичної мембрани та індукувати негеномні дії, зокрема, стимуляцію кишкового транспорту Кальцію.

Вітамін D є стероїдною речовиною, що необхідна всім хребетним тваринам для підтримки метаболізму Кальцію і Фосфору в оптимальних межах, здорового скелета, скорочення м'язів, модуляції росту клітин та нервово-м'язової функції. Кальциферол також регулює діяльність імунної системи, пригнічує розвиток патологічних клітин, ангіогенез та запальні реакції. Активна форма вітаміну D – 1,25 $(OH)_2 D_3$ стимулює кишкове всмоктування, ниркову реабсорбцію Са і підтримує його мінімально фізіологічний рівень у крові.

Дефіцит вітаміну D у кіз спричинює зниження кишкової та ниркової реабсорбції Кальцію, що призводить до підвищення рівня паратиреоїдного гормону. Цей процес зумовлює активацію остеоцитів і, як наслідок, прискорює демінералізацію кісткової тканини, спричинюючи розвиток багатьох захворювань у дорослого поголів'я, зокрема, аліментарної та фіброзної остеодистрофії, вторинної остеодистрофії, дисфункції залоз внутрішньої секреції, а також рахіту у молодняку. Розвиток нескелетних патологій, зокрема, запальних, неопластичних та аутоімунних захворювань також пов'язують із дефіцитом холекальциферолу в організмі. Окрім того, порушення D-вітамінного та кальцієво-фосфорного метаболізму у кіз є причиною

розвитку післяродової гіпокальціємії та післяродової гіпофосфатемії.

В організмі тварин гомеостаз Кальцію і Фосфору підтримується взаємодією всмоктування та реабсорбцією через шлунково-кишковий канал і нирки, а також за зберігання та мобілізацію з кісткової тканини і регулюється, переважно, біологічно активними метаболітами холекальциферолу – 25OH D_3, 1,25 $(OH)_2$ D_3, а також паратгормоном (ПТГ; синтезується прищитоподібними залозами) і кальцитоніном (КТ; утворюється спарафолікулярними (світлими) С-клітинами щитоподібної залози) і фактором росту фібробластів-23 (FGF23).

На відміну від моногастричних тварин, дрібні жуйні не модулюют ниркову екскрецію Кальцію у відповідь на його обмеження в кормі. Мобілізація Са і Р із скелету стимулюється ПТГ через активацію остеокластів, опосередковану через рецепторний активатор ядерного фактора (RANK). Вітамін D підтримує гомеостаз Са (завдяки стимуляції СаЗБ) і Р (доведена пряма швидка дія 1,25 $(OH)_2$ D_3 через безпосередній вплив на процеси абсорбції цих життєво важливих елементів у кишечнику, реабсорбцію цих катіонів у ниркових канальцях та мобілізацію їх із кісткової тканини).

Фосфор є складовою аденозинтрифосфату (АТФ) та нуклеотидів. Макроергічні фосфатні сполуки, серед яких основною є аденозинтрифосфатна кислота, забезпечують як накопичення запасів енергії, так і її витрати (АТФ, АДФ, креатинфосфат), впливаючи на білковий, ліпідний, вуглеводний, мінеральний, енергетичний метаболізми. Виявлено взаємодію між вітаміном D і фактором росту фібробластів 23 (FGF23), кістковим гормоном, що спричиняє розвиток фосфатурії і знижує синтез 1,25 $(OH)_2$ D_3.

Незважаючи на різновекторність етіологічних факторів, загальним для усіх форм остеодистрофії є порушення процесів утворення та оновлення кісткової тканини, яке проявляється посиленою мобілізацією з неї Кальцію, Фосфору та інших елементів, тому патологія супроводжується остеомаляцією, остеопорозом та остеофіброзом, порушенням механізму підтримання їх гомеостазу. Основними чинниками остеодистрофії у тварин є порушення годівлі та гіподинамія, а провідними ланками її патогенезу − дисбаланс між формуванням і резорбцією кістки.

Основними методами діагностики порушень D-вітамінного та кальцієво-фосфорного метаболізму у кіз є клінічні, фізичні, біохімічні, імуноферментні та патолого-морфологічні дослідження. За біохімічного аналізу в сироватці крові кіз визначають уміст загального Кальцію, неорганічного Фосфору, активність лужної фосфатази та її ізоферментів, а за імуноферментного – концентрацію 25OH D_3, 1,25$(OH)_2$ D_3, кальцитоніну і паратиреоїдного гормону.

Ключові слова: кози, вітамін D, метаболіти, метаболізм, Кальцій, Фосфор, печінка, нирки.

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