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BIOCHEMICAL MARKERS OF CONNECTIVE TISSUE IN THE PATHOGENESIS OF GASTROENTERITIS IN DOGS AND CATS

Dmytro Morozenko, Yevheniia Vashchyk, Nadiia Kononenko, Andriy Zakhariev, Nataliia Seliukova, Dmytro Berezhnyi, Kateryna Gliebova, Valentyna Chikitkina

The aim: *to analyze and establish the pathogenetic role of biochemical markers of the state of connective tissue in diseases of the stomach and intestines in dogs and cats.*
Materials and methods. *The research was carried out by the method of analysis of sources of scientific literature (PubMed, Elsevier, electronic resources of the V. I. Vernadskyi National Library), because of which a scheme of the pathogenesis of gastroenteritis in dogs and cats with the participation of connective tissue biopolymers was created.*
Results. *In dogs and cats, the issue of the use of biochemical markers for the diagnosis of diseases of the stomach and intestines has not yet been fully clarified. It is known, that in dogs and cats, lymphocytic-plasmacytic enteritis is histologically determined by fibrosis of the intestinal wall, but biochemical tests for the diagnosis of this condition are not given. Among the biochemical markers of inflammatory bowel disease, tumor necrosis factor, C-reactive protein and microalbumin were identified. Although C-reactive protein was elevated in a greater number of diseased animals, this increase was insignificant. Other tests also did not show high diagnostic informativeness. Several stages can be identified in the pathogenesis of alimentary gastroenteritis in dogs and cats. First, the irritating components of food act on the mucous membrane of the stomach and disrupt its secretory and motor functions, which causes gastritis. Thus, the use of indicators of the state of connective tissue in the diagnosis of intestinal diseases in dogs can be used to assess the degree of the inflammatory process.*
Conclusions. *According to the results of the analysis, it was established, that the development of the inflammatory process in the stomach and intestines causes an increase in the content of glycoproteins in the blood serum of cats and dogs, and a decrease in synthetic processes in the liver is accompanied by a decrease in the concentration of glycosaminoglycans (GAG) in the blood serum of sick animals. It should be noted, that this decrease has peculiarities: in dogs, the content of total chondroitin sulfates remained at the level of clinically healthy animals, while the concentration of total GAG decreased. In cats, on the contrary, the content of total chondroitin sulfates decreased, and the fractional composition of GAG remained unchanged. The level of excretion of oxyproline and uronic acids in the urine of animals with gastroenteritis did not change, which indicates the absence of catabolism of collagen and proteoglycans with gastroenteritis*
Keywords: *dogs, cats, gastroenteritis, connective tissue, biochemical markers, pathogenesis, glycoproteins, glycosaminoglycans, chondroitin sulfates, oxyproline, uronic acids*

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1. Introduction

In human medicine, there is a significant number of scientific works on the state of connective tissue biopolymers in diseases of the stomach and small (gastritis, gastroduodenitis) and large (colitis, proctitis) intestines [1, 2]. The role of hyaluronic acid in intestinal pathology is especially important [3]. The study of the structural organization of the mucous membrane in atrophic gastritis showed that in the case of a combination with signs of connective tissue dysplasia, the atrophic process is characterized by a high frequency of mucoidization and cystic transformation of the fundal glands, a pronounced and uneven decrease in their density in both parts of the stomach with a high density of blood vessels. This organization of the mucous membrane can testify to its dysplasia and reflect the presence of a peculiar gastropathy due to undifferentiated connective tissue dysplasia [4, 5]. The mucous membranes of the stomach and duodenum have a single protective mechanism, which includes mucus gel and bicarbonate secretion. Violation of the mucous barrier can lead to damage to the mucous membrane, a decrease in the level of fucose, sialic acids, and the content of neutral and acidic mucopolysaccharides. An increase in the content of glycosaminoglycans (GAG) in histological preparations of the stomach of rats with ulcers, treated with antacids, indicates stimulation of GAG synthesis [6]. The latter play an important role in mucus formation and are a necessary component for the formation of mature collagen and, accordingly, the ulcer scarring process during the normal course of the process [7]. In addition, an increase in the relative area of collagen fibers, as well as a decrease in the number of cellular elements in the

granulation tissue [8] were noted as a confirmation of the stimulating effect of polysaccharides on the healing process of a chronic ulcer. In dogs and cats, clinical-pathogenetic disorders of the metabolism of connective tissue due to diseases of the gastrointestinal tract are currently an understudied issue compared to humane medicine [9]. This determines the relevance of our research.

The aim of the research to analyze and establish the pathogenetic role of biochemical markers of the state of connective tissue in diseases of the stomach and intestines in dogs and cats.

2. Materials and methods

The research was carried out by the method of analysis of sources of scientific literature (PubMed, Elsevier, electronic resources of the V. I. Vernadskyi National Library), because of which a scheme of the pathogenesis of gastroenteritis in dogs and cats with the participation of connective tissue biopolymers was created.

3. Research results

Dysplasia of connective tissue increases the influence on the formation and course of inflammatory diseases of the stomach and duodenum, namely, it accelerates their development, increases the frequency of exacerbations, the extent and depth of lesions of the mucous membrane, and contributes to the formation of destructive processes. Against the background of connective tissue dysplasia, gastroduodenal diseases in most cases are combined with the pathology of various parts of the digestive tract, the structure of which is dominated by caries, dyskinesia of the gallbladder, chronic constipation, and chronic colitis [10].

Studies of the metabolism of connective tissue in gastroesophageal reflux disease indicate that metabolites of connective tissue (GAG and oxyproline) are adequate "witnesses" of the chronic inflammatory process in any organ and tissue, and can act as biochemical markers of its various stages. Therefore, the content of GAG in the gastric juice of patients with erosive esophagitis correlates with the level of connective tissue oxyproline. The direction of changes in the content of GAG and protein-bound oxyproline suggests that the content of GAG in this contingent of patients reflects the course and expressiveness of reparative processes in the lower third of the esophagus. The exacerbation phase of gastroesophageal reflux disease is characterized by a dissociation between a high level of biochemical indicators, characterizing the destruction of connective tissue (elastase), and a relatively low content of indicators responsible for collagen synthesis processes (protein-bound oxyproline). Thus, an increased level of protein-bound oxyproline against the background of depression of destruction indicators (elastase and free oxyproline of gastric juice) characterizes the remission of gastroesophageal reflux disease, which makes it possible to give an operative assessment of the state of health and predict the end of the disease [11].

During an exacerbation of erosive gastroduodenitis, the ratio of sialo- to fucoglycoproteins in the gastric juice increases, which leads to destabilization of the protective functions of the mucous membranes, and the level of mannosidase in blood serum probably correlates with the large diameter of erosions and the presence of multiple erosions. In erosive gastroduodenitis in children, associated with dysplasia of connective tissue, there is a decrease in the protective functions of the mucous membranes, caused by a lack of sialic and sulfated mucins [12]. Thus, we can talk about certain features of the course of diseases of the upper part of the gastrointestinal tract in children with connective tissue dysplasia. It was found, that children have a tendency to recurrent and chronic inflammatory diseases of the stomach and duodenum. At the same time, there is a functional insufficiency of fibroblasts, which is manifested by a violation of GAG exchange and a deficiency of certain types of collagen, which can lead to a slowdown in regeneration and destabilization of the protective function of the mucous membrane [13].

It is known, that glycoproteins of the gastric mucosa are important in the pathogenesis of chronic gastritis. There are certain features of glycoprotein secretion in the gastric mucosa of carnivores and humans: the surface epithelium of the stomach of carnivorous animals, in addition to neutral glycoproteins, synthesizes sialo- and sulfoglycoproteins, which additionally protect the mucous membrane from self-digestion. These substances have properties to directly inactivate pepsin, reducing its proteolytic capabilities. Thus, the mucous membrane in dogs and cats, unlike humans, has a more powerful protective barrier, which affects the pathogenesis of gastritis [14].

Research by a group of scientists [15, 16] determined diagnostic criteria and pathological changes in the intestinal mucosa for duodenal ulcer disease against the background of connective tissue dysplasia. It has been found, that duodenal ulcer due to connective tissue dysplasia develops in conditions of impaired fixation of the stomach and duodenum, volume ratios of these organs, duodenogastric reflux and lower rates of gastric secretion, associated with subatrophic and atrophic changes in the mucous membrane, caused by connective tissue dysplasia. Microscopic examination of biopsies of the gastric mucosa revealed a number of changes in loose connective tissue: the orderliness of collagen structures was disrupted in the form of the appearance of separate areas of connective tissue replacement by less differentiated ligaments, as well as the formation of sclerotic processes. Accumulation of sulfated and non-sulfated GAG was also observed in the stomach tissues.

Studies of the biochemical composition of gastric mucus during the development of gastric cancer showed that the content of the protein part of mucus glycoproteins, galactose, nucleic acids and pepsin activity increased in gastric mucus; Signet ring cell cancer, unlike adenocarcinoma, is characterized by a lower content of hexosamines and sialic acid in the structure of glycoproteins with an increase in the level of nucleic acids, bicarbonates and pepsin. A study of the biochemical composition of gastric wall mucus revealed that in dysplasia there is a decrease in the concentration of total monosugars due to a sudden decrease in the content of hexosamines. Due to the fact that hexosamines are part of the body monosaccharides and determine the number and length of carbohydrate chains of glycoproteins, it can be assumed, that the glycosylation of the glycoprotein complex is inhibited, defective glycoproteins are synthesized, as a result of which the gelling properties of mucus de-

crease and its protective properties decrease. The increase in the content of sialic acids, which is observed in this case, has a compensatory nature, because it contributes to the formation of intermolecular bonds and leads to the thickening of mucus [17, 18]. The composition of human mucus, secreted by the cells of the mucous membranes of the stomach and intestines, necessarily includes specific glycoproteins – mucins. Each mucin, secreted by the gastric mucosa, contains four subunits, connected by disulfide bridges. Mucus forms a flexible gel that covers the mucous membrane. The occurrence of gastric and duodenal ulcers is primarily associated with a violation of the protective mucous barrier. The composition of mucins, secreted in the intestines, is different in people with tumors of the small intestine and patients with ulcerative colitis compared to healthy people [19, 20].

Violation of the metabolism of connective tissue also occurs due to damage to the lower parts of the gastrointestinal tract. The conducted studies allow us to assume the activation of collagen fiber formation processes during the period of remission in non-specific ulcerative colitis. It is possible that the activation of the development of connective tissue may be determined by the imperfection of the processes of collagen synthesis against the background of a decrease in general and local immunity and the restructuring of the intestinal mucosa. Nonspecific ulcerative colitis in the exacerbation phase is characterized by high elastolytic activity, an increase in the content of GAG and protein-bound oxyproline in the blood. The absence of perforation of the large intestine in most patients with nonspecific ulcerative colitis can be explained by the limited spread of the inflammatory-destructive process in the deeper layers of the wall of the large intestine due to active reparative processes, the biochemical marker of which is protein-bound oxyproline and GAG. This makes it possible to use this indicator as an additional diagnostic criterion for inflammatory and functional pathology of the large intestine [3].

There are also data on the influence of connective tissue dysplasia on the structural and functional state of the colon in irritable bowel syndrome. It was proved, that the presence of connective tissue dysplasia syndrome affects the functioning of the large intestine, which is manifested by a violation of the motor-evacuation function of the gastrointestinal tract [21].

With destructive intestinal diseases, the content of free and peptidose-bound oxyproline in the blood plasma of patients increases. Activation of collagen degradation was accompanied by increased collagen synthesis, as evidenced by an increase in the content of protein-bound oxyproline. In the undifferentiated form of non-specific ulcerative colitis, patients were found in whom the activity of proteinase inhibitors was reduced, which is the basis for excessive activation of proteinases and collagen degradation. In intestinal biopsies, collagen degradation was stimulated in the area of ulcers. The most pronounced imbalance of collagen synthesis and breakdown was during Crohn's disease. Patients with ulcerative colitis were found to have increased collagen degradation in the intestinal tissue. Determining the content of hydroxyproline fractions can be an additional criterion for assessing the severity of destructive intestinal diseases and the risk of developing complications [22].

The presence of connective tissue dysplasia in humans determines the features of the clinical picture of irritable bowel syndrome, the development of inflammatory changes in the mucous membrane of the distal part of the large intestine. An increase in the concentration of GAG and indicators of lipid peroxidation are biochemical markers of the development of inflammatory changes in the rectal mucosa [23].

In dogs and cats, the issue of the use of biochemical markers for the diagnosis of diseases of the stomach and intestines has not yet been fully clarified. According to K. Yamasaki et al. [24], in dogs and cats for lymphocytic-plasmacytic enteritis, fibrosis of the intestinal wall is histologically determined, but biochemical tests for the diagnosis of this condition are not given. Based on the results of research by T. M. McCann et al. [25], tumor necrosis factor, C-reactive protein, and microalbumin were identified as biochemical markers of inflammatory bowel disease. Although C-reactive protein was elevated in a greater number of diseased animals, this increase was insignificant. Other tests also did not show high diagnostic informativeness.

Thus, the use of indicators of the state of connective tissue in the diagnosis of intestinal diseases in dogs can be used to assess the degree of the inflammatory process.

Several stages can be identified in the pathogenesis of alimentary gastroenteritis in dogs and cats. First, the irritating components of food act on the mucous membrane of the stomach and disrupt its secretory and motor functions, which causes gastritis (Fig. 1).

Later, as a result of changes in the concentration of hormones and peptides in the gastrointestinal tract, enterogastric, enterohepatic, enterocholekinetic, and enteropancreatic connections are disrupted, which causes inflammation of the intestinal mucosa. During the development of gastroenteritis, there is a violation of digestion and absorption of nutrients, which is manifested by their maldigestion and malabsorption. It is possible that the deficiency of amino acids and carbohydrates in the body of sick animals causes a decrease in synthetic processes in the liver, which is manifested not only by hypoalbuminemia, but also by a decrease in the synthesis of proteoglycans.

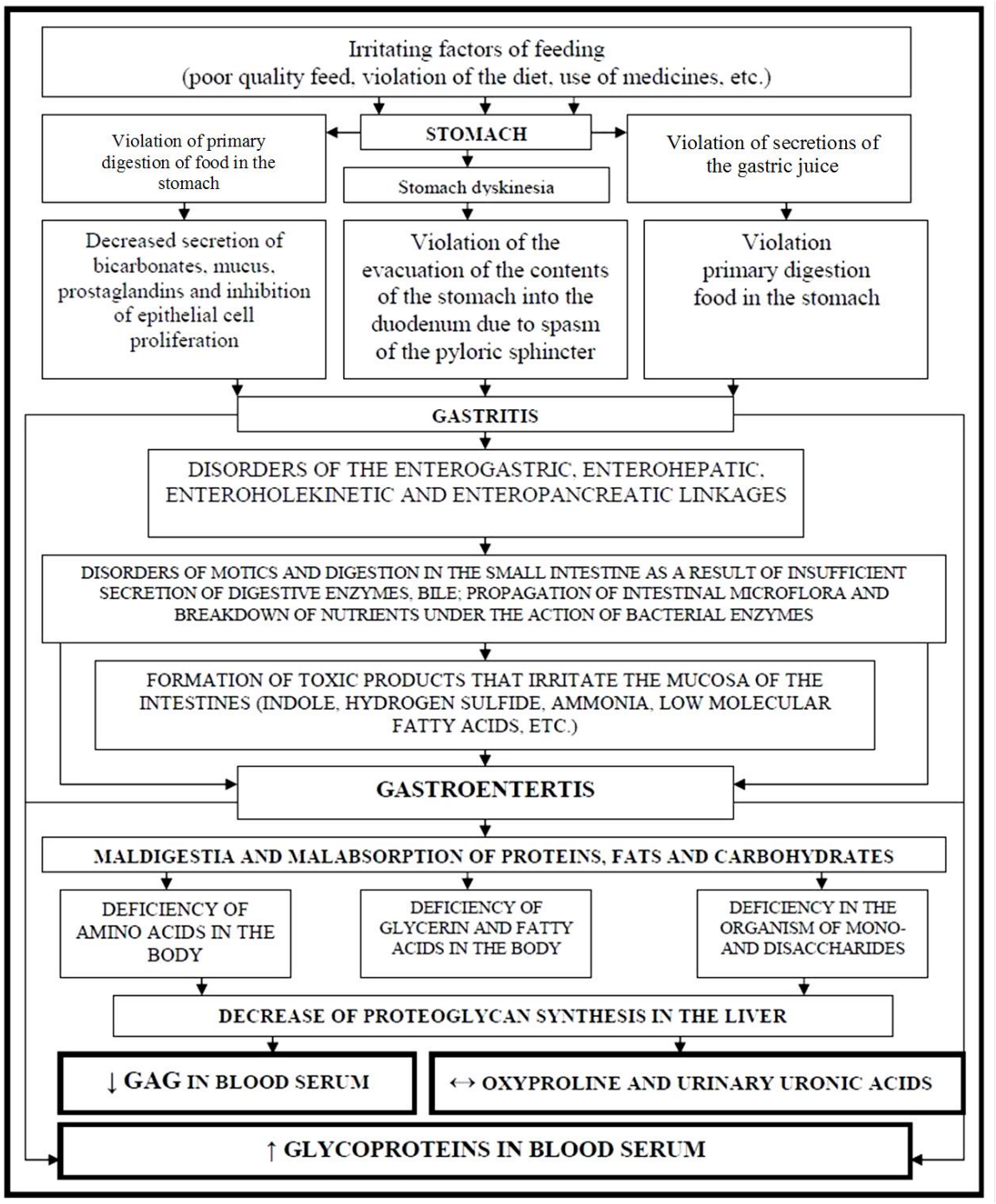

Fig. 1. Pathogenetic role of connective tissue metabolism disorders in gastroenteritis of dogs and cats: ↑ – growth of the indicator; ↓ – reduction of the indicator; ↔ is a normal indicator

Later, as a result of changes in the concentration of hormones and peptides in the gastrointestinal tract, enterogastric, enterohepatic, enterocholekinetic, and enteropancreatic connections are disrupted, which causes inflammation of the intestinal mucosa. During the development of gastroenteritis, there is a violation of digestion and absorption of nutrients, which is manifested by their maldigestion and malabsorption. It is possible that the deficiency of amino acids and carbohydrates in the body of sick animals causes a decrease in synthetic processes in the liver, which is manifested not only by hypoalbuminemia, but also by a decrease in the synthesis of proteoglycans.

Research limitations. The studies were analytical in nature and based on literary sources that reflected the pathogenesis and role of connective tissue biopolymers in diseases of the stomach and intestines, in particular, in dogs and cats.

Prospects for further research. A promising direction of research is the study of the distribution and clinical-pathogenetic mechanisms of diseases of the stomach and intestines in dogs and cats with the determination of the most informative diagnostic markers.

4. Conclusions

According to the results of the analysis, it was established, that the development of the inflammatory process in the stomach and intestines causes an increase in the content of glycoproteins in the blood se-

rum of cats and dogs, and a decrease in synthetic processes in the liver is accompanied by a decrease in the concentration of GAG in the blood serum of sick animals. It should be noted, that this decrease has peculiarities: in dogs, the content of total chondroitin sulfates remained at the level of clinically healthy animals, while the concentration of total GAG decreased. In cats, on the contrary, the content of total chondroitin sulfates decreased, and the fractional composition of GAG remained unchanged. The level of excretion of oxyproline and uronic acids in the urine of animals with gastroenteritis did not change, which indicates the absence of catabolism of collagen and proteoglycans with gastroenteritis.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results, presented in this article.

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Dmytro Morozenko*, Doctor of Veterinary Sciences, Senior Researcher, Head of Department, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Yevheniia Vashchyk, Doctor of Veterinary Sciences, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Nadiia Kononenko, Doctor of Medical Sciences, Professor, Head of Department, Department of Physiology and Pathological Physiology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Andriy Zakhariev, PhD, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Nataliia Seliukova, Doctor of Biological Sciences, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Dmytro Berezhnyi, PhD, Associate Professor, Department of Veterinary Medicine and Pharmacy, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Kateryna Gliebova, PhD, Senior Researcher, Associate Professor, Department of Physiology and Pathological Physiology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

Valentyna Chikitkina, PhD, Associate Professor, Department of Physiology and Pathological Physiology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002

***Corresponding author:** Dmytro Morozenko, e-mail: d.moroz.vet@gmail.com*