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Condition of the Gastrointestinal Tract in Rheumatological Patients

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Abstract:
In rheumatological practice, nonsteroidal anti-inflammatory drugs (NSAIDs) remain of great importance in the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), osteoarthrosis (OA), gout, etc., the widespread use of which is due to the relief of pain and inflammation, which are the main clinical manifestations of rheumatological diseases (RH). At the same time, it is reliably known that regular use of NSAIDs is associated with a number of side effects and risks, the leader of which is inflammatory, erosive, and ulcerative changes in the mucous membrane of the gastrointestinal tract (GIT) [13, 14]. One of the unresolved issues is the occurrence of secondary damage from the gastrointestinal tract (GI).

Keywords: rheumatological diseases, gastrointestinal tract, NVPP, corticosteroids, apoptosis, proliferation, gastric mucosal epithelial cells.

Introduction

Tens of thousands of scientific papers are devoted to the mechanisms of apoptosis development. At present, a huge amount of material has been accumulated that testifies to the role of the processes of proliferation and programmed cell death in maintaining the structural integrity of the gastric mucosa. Structural homeostasis (homeomorphosis) of tissues is ensured by the equilibrium between cell neoplasm (mitosis) and cell death (apoptosis). Apoptosis plays a huge role in the homeostatic control of the dynamic balance between cell proliferation and elimination, its initiation and maintenance are controlled by the corresponding anti- and pro-apoptotic factors, among which the main regulatory role is assigned to p53, Bcl-2 and PUMA [3,4]. The predominance of mitosis leads to hyperplasia, the predominance of apoptosis leads to atrophy [1].

It is known that gastroduodenal complications often occur in rheumatological patients [5], which significantly affect the course and results of treatment of rheumatological patients [7]. Perhaps this is due to the negative effect of drugs used to treat this category of patients. The study of the state of cellular renewal in the stomach and in rheumatological patients is also important from the point of view of the fact that a wide arsenal of drugs used for the treatment (NSAIDs, corticosteroids, etc.) of rheumatological patients is potentially dangerous due to the development of gastroduodenal side effects.

Objective:

To study the state of the gastrointestinal tract in patients with RH: to conduct a comparative analysis of the relative content of epithelial cells undergoing necrosis, the value of the mitotic and apoptotic indices in the gastric mucosa in an equivalent number of patients with rheumatological diseases at the onset of the disease and against the background of treatment with NSAIDs and DPC BU.

Materials and Methods

To assess the primary lesion of the gastrointestinal tract in the Republic of Belarus, the examined patients were divided into 2 groups: group 1 - newly diagnosed patients (onset of the disease), group 2 - patients with a certain history of RH (re-infected and previously treated with NSAIDs and other drugs). The paper also presents the results of a comprehensive screening examination of 40 patients with rheumatological diseases (RH), including 20 patients at the onset of the disease. 20 patients with a history of 1 to 10 years or more. The control group consisted of 20 patients with duodenal ulcer disease (DPC). All three groups of patients were comparable in terms of gender and age.

The determination of markers of proliferation and apoptosis was carried out by the immunohistochemical method. Immunohistochemical methods were used to determine apoptosis and proliferation. For this purpose, biopsy material in the amount of 60 samples taken from the antral part of the stomach (in 40 patients with rheumatological diseases and 20 in patients with duodenal ulcer) was used. The treatment of the biomaterial was carried out according to standard histological methods with pouring into paraffin.

To determine the level of expression of the p53 protein as primary monoclonal antibodies (MCAT), p53 (DO-7 clone) of Dakopatts (Denmark) was used, to assess PCNA activity, PCNA (MS-10 clone) of Dakopatts (Denmark) was used. The results of p53 and PCNA protein expression were evaluated by the percentage of positively responding cells per 500 analyzed. The apoptosis index (AP) was defined as the number of stained bodies divided by 1000 cells and multiplied by 100%, and the mitotic index (MI) was calculated as the number of stained nuclei divided by 500 cells and multiplied by 100%.

The obtained data were statistically processed on a Pentium I computer using the Statgrafics software package (USA). The significance of the differences (P) was calculated using the t-Student's test. The differences were considered significant at $P < 0.05$. The research was carried out in the Laboratory of Genetics of the Russian Scientific Research Center of the Ministry of Health of the Republic of Uzbekistan.

Research Results and Discussion

At the same time, the study of clinical gastrointestinal symptoms at the onset of the disease revealed that such manifestations of dyspeptic syndrome as: heartburn,

bitterness in the mouth, heaviness in the epigastric region were equally common, in every fourth patient. Symptoms of lesions of the distal parts of the digestive tube, such as flatulence, constipation, diarrhea and cramping pain associated with bowel movements, occurred in 25%, 25%, 20% and 30% of the examined patients, respectively. At the same time, in patients with BU DPC (control group), the structure of clinical symptoms is dominated by pain syndrome, which occurs in almost 100% of patients, and symptoms such as heartburn and bitterness in the mouth are rare than in patients with the onset of RH. In addition, the symptoms of intestinal involvement are also less common in patients with BU DPC. They practically do not have diarrhea, and the frequency of flatulence and cramping pain associated with bowel movements is noticeably less than in patients with the onset of RH. From the presented data, it becomes obvious that in the conditions of the onset of RH, there are certain shifts in the functional activity of the gastrointestinal tract, and not only on the part of its proximal, but also in its distal parts. At the same time, the symptom complex on the side of the digestive tract is not identical to the symptom complex that takes place in BU DPC. A distinctive feature of the manifestations of gastrointestinal lesions at the onset of RH is the presence of frequent signs of involvement of the large intestine in the pathological process. The reason for this fact also remains unclear.

The study of clinical gastrointestinal symptoms in patients with RH with a certain anamnesis (group 2 patients) indicates an increase in the frequency of occurrence of the analyzed symptoms compared to the onset of the disease (group 1 patients). At the same time, not only does the frequency of symptoms such as heartburn, abdominal pain, epigastric heaviness, flatulence and others increase, but also symptoms appear that were absent among patients with the onset of RH. Consequently, as the duration of RH prolongs, the frequency and severity of gastrointestinal symptoms increases. A distinctive feature of the gastrointestinal symptom complex in patients with a long-term history of RH is a certain "smoothing" of manifestations on the part of the distal parts of the digestive tube. Apparently, in the mechanisms of increasing gastrointestinal symptoms in this category of patients, the priority role is played by drugs used in the treatment of RH and, first of all, NSAIDs.

In this study, we also studied the death and proliferation of gastric mucosa cells in rheumatological patients at the onset of the disease and against the background of NSAID treatment.

As can be seen from the data presented in Talitsa 1, the mitotic index (MI) in rheumatological patients was 0.6±0.1%, in patients with BU this indicator was 3.5 times higher. The apoptosis index in patients with BU was also 1.6-fold higher than in rheumatological patients. Consequently, in rheumatological patients in the gastric mucosa, epithelial cells undergo apoptosis to a lesser extent than in patients with BU. A similar pattern can be traced with regard to proliferation. If we take into account the fact that in normal gastric cells the apoptosis index (AI) is about 3% [1], in

rheumatological patients the death of epithelial cells in this way is higher (1.6 times) than in healthy people, which indicates the stimulation of apoptosis in RB.

Table 1 **Some Indicators of Cell Renewal in the Gastric Mucosa in Rheumatological Patients**

Patient groups	Indicators				
	MI (Mitotic index n=6000v%)	AI (Apaptotic index in n=5000%)	Necrosis % n=3000	Factors	
				AI/MI	AI/necrosis
Peptic ulcer disease (control)	2.1± 0.2	8.0± 0.5	2.4± 0.3	3,8	3,3
Rheumatologists For example, if you want to be a member of a group	0.6± 0.1	4.9± 0.4	1.6± 0.2	8,2	3,1
*P	<0.05	<0.05	<0.05≤P<0.1		

Note: * P <0.05 compared to control.

The study of the ratio of apoptosis and mitosis (proliferation) of epithelial cells in the studied groups of patients shows that if the values of this ratio in rheumatological patients is 8.2, then in patients with BU it is 3.8, respectively. Consequently, the studied coefficient is 2.2 times higher in rheumatological patients.

Taking into account that under physiological conditions the equilibrium between the process of proliferation and cell death must be maintained, it becomes obvious that in the conditions of both rheumatological diseases and peptic ulcer disease, this ratio is violated, due to the predominant activation of the processes of cell death. This can undoubtedly lead to a cellular deficiency of the gastric mucosa and is fraught with the danger of developing atrophic gastritis [9]. The results obtained show that the imbalance between epithelial cell renewal and death is more pronounced in rheumatological patients than in BU. Apparently, this is due to the fact that in conditions of increased death of gastric mucosa cells by apoptosis, there is a more pronounced stimulation of proliferative processes, and new, young epithelial cells are formed from the germinal zone. This is possible if there is a sufficient compensatory capacity of the growth zone of the mucous membrane. And in the conditions of rheumatological patients, due to the potential systemic damage to the connective tissue structures of the stomach, the germinal zone may initially suffer, and hence the intensity of proliferative processes is relatively low.

It is known that there are two pathways of cell death: apoptosis and necrosis [8]. The path of death "chosen" by the damaged cell depends on many factors, including the type of cell, its energy status, the nature and degree of damage, the state of the body's immune system, etc. [10].

Taking into account that in the conditions of the pathologies under study, especially in ulcerative lesions of the DPC, there are a number of factors damaging the epithelium of the gastric mucosa, leading to cell death like necrosis. We separately analyzed the

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characteristics of necrobiotic processes of the gastric mucosa in the studied groups of patients.

As can be seen from the data presented in Table 1, the proportion of cells undergoing necrosis in rheumatological patients is $1.6 \pm 0.2\%$, and in patients with BU this indicator is 1.5 times higher.

Consequently, in the conditions of both rheumatological diseases and BU in the gastric mucosa, cells die by necrosis, and this is comparatively pronounced in patients with BU. If we take into account the fact that necrosis, unlike apoptosis, is only a manifestation of a pathological process, it becomes clear that in the conditions of rheumatological diseases, although the locus of primary attack is "far away" from the gastric mucosa, there is damage to the epithelial lining of this organ.

Interesting results were obtained in the analysis of the AI/necrosis ratio, despite the presence of clear differences between the compared groups, both in terms of necrosis and apoptosis, the AI/necrosis ratio was almost the same in both groups of patients. This indicates that regardless of the number of cells affected by death, the ratio of the two cell death pathways remains unchanged. This is fully consistent with the opinion of C.J. Zeiss [380] that there is a so-called "apoptotic-necrotic continuum" determined by cross-interactions between cell death reactions and homeostasis conservation.

It is known that the process of programmed cell death is regulated in a complex way through humoral factors, glucocorticoids, cytokines, and there is also gene regulation carried out through special regulatory proteins [11,12]. Among the special proteins that regulate programmed death, the p53 protein plays a central role [6]. This protein regulates the expression of genes involved in cell cycle blockade or interacts with proteins involved in programmed cell death.

In this regard, the expression of the p53 protein in gastric epithelial cells was studied to assess the readiness of apoptosis cells in RB. The results of these studies are presented in Table 2.

Table 2 **Expression of p53 protein in the gastric mucosa in rheumatological patients.**

Patient groups	Qty Samples	Positive expression of p53 protein	
		Number of positive observations	Frequency of p53 positive cells, in % n=500
Rheumatological diseases:			
In the opening	20	1	14,00+1,55
against the background of NSAIDs	20	13	61,60+2,2 *
Peptic ulcer disease (control)	20	10	16,30+1,65

Note: * P <0.05 compared to control.

As can be seen, in RB at the onset of the disease, a positive reaction to the p53 protein is observed only in one case out of 20 cases, which is 5%. At the same time, in the

stomach of patients with BP DPC, a positive reaction to the p53 protein is observed in 50% of cases. In the Republic of Belarus, which have a certain "experience", against the background of therapy with anti-inflammatory drugs, this figure reaches up to 65%. Consequently, in patients with a sufficient history and receiving symptomatic therapy, cells with a positive reaction to the presence of the p53 protein are significantly more common in the gastric mucosa.

The study of the level of expression of the p53 protein in gastric epithelial cells shows (Table 2) that the level of expression of this pro-apoptotic protein in RB at the onset of the disease is almost comparable to the level in patients with BU. However, as the duration of the disease increases and anti-inflammatory drugs are taken, the level of expression of the p53 protein increases by 4.4 times compared to the onset of the disease. Consequently, RB has a high level of expression of the pro-apaptotic protein p53 in the gastric mucosa. Even in the conditions of the "debut" of the disease, the expression of this protein in the cells of the gastric mucosa in rheumatological patients is comparable to that of BU. As the duration of the disease lengthens and NSAIDs are taken, the number of cells with degraded DNA and prepared for programmed death increases, since it is the p53 protein that has the ability to prevent the fixation of genetic damage and initiate apoptosis in cells with DNA defects.

It is known that, despite the similarity of some destructive processes in apoptosis and necrosis, the principal difference of apoptosis is the presence of genetic control and specific proteins regulating the apoptotic process [8]. Therefore, apoptotic cell death is also called programmed cell death, which is designed to maintain the constancy of the number and culling of defective cells. Apoptosis in a healthy organism is balanced by its physiological regeneration. At the same time, the process of regeneration, like apoptosis, is also programmed and genetically controlled. One of the markers of this control is the expression of the PCNA protein.

We also studied the expression of the PCNA protein in the gastric mucosa cells of patients with RB. As can be seen from Table 3, in the conditions of the pathology under study, both at the onset and against the background of NSAID treatment, a positive reaction to the presence of PCNA protein is noted in all the presented samples of the gastric mucosa. A similar pattern can be traced in the samples obtained from patients with BU DPC.

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Table 3 **Expression of PCNA protein in the gastric mucosa in rheumatological patients.**

Patient groups	Qty Samples	Positive expression of PCNA protein	
		Number of positive observations	Frequency of PCNA positive cells, in % n=500
Rheumatological diseases: In the opening	20	20	95.20± 0.96*
against the background of NSAIDs	20	20	78.5±1.8
Peptic ulcer disease (control)	20	20	82.1±1.7

Note: * P <0.05 compared to control.

Analysis of the level of PCNA protein expression in gastric epithelial cells shows that if the values of the studied indicator at the onset of rheumatological diseases are 95.2 ± 0.96%, then in patients with "experience" of the disease, against the background of NSAID therapy, it decreases by 18%.

Consequently, as the disease becomes "chronic", there is a decrease in the expression of the PCNA protein, a marker of regeneration or proliferation in the epithelial cells of the stomach, and the gastric mucosa becomes less viable for cellular renewal than at the onset of the disease. This is evidenced by the increase in the AI/MI coefficient in RB much higher than unity, i.e. there is an imbalance between the death of epithelial cells and their regeneration. It should also be noted that if the level of expression of the PCNA protein in gastric mucosa cells at the onset of rheumatological diseases is 16% higher than that in peptic ulcer disease, then in RB with "experience" on the background of NSAID therapy, this indicator is almost comparable to the results in peptic ulcer disease (Table 3). At the same time, the mitotic index in RB, as shown by our results (Table 1), is 3.5 times lower than in patients with BU.

Thus, the results of the studies indicate that in RB in the gastric mucosa there is an activation of epithelial apoptosis, which becomes more pronounced against the background of anti-inflammatory therapy. At the same time, between the process of cell death and the process of regeneration, the balance in the gastric mucosa is disturbed, due to the predominance of apoptosis over mitosis. In general, disturbances in the processes of cellular renewal in the gastric mucosa in RB at the onset of the disease are comparable to such disorders occurring in patients with BU. And in the conditions of rheumatological diseases with a relatively long course (against the background of the use of NSAIDs), disturbances in the processes of cellular renewal in the gastric mucosa become more pronounced than in patients with BU.

Therefore, from the morphological studies of the gastrointestinal tract in the Republic of Belarus, it should be noted that, in principle, the revealed disorders, as well as clinical and functional signs, are similar to those disorders that occur in patients with gastrointestinal diseases, in particular, the GD zone. At the same time, only quantitative

differences are noted depending on the duration of the course of the disease. However, here it is necessary to pay attention to the genesis of the occurrence of these structural disorders. It can be assumed that in patients with RH at onset, in contrast to gastrointestinal diseases, the locus of primary lesions is not in the parenchyma (epithelial) cell, but in the stroma, which is inhibited as RH progresses, affecting the germinal zone, exhausting its proliferative potential, and has an indirect effect on parenchymal cells. This, apparently, is why in the initial stages of the development of gastrointestinal tract in the mucosa, changes of a predominantly dystrophic nature are traced, without visible destruction. And as the anamnesis becomes longer, these changes deepen, and the drugs used have a direct cytodestructive effect on the "exposed" epithelial cells of the gastrointestinal tract. Consequently, in RB with a long-term course of parenchyma (epithelial layer), the gastrointestinal tract is "attacked" from two sides: from the side of the connective tissue stroma (ongoing antigenic attack) and from the outside, from the side of the cavity, the digestive tube (aggressive effect of drugs – NSAIDs). This is also confirmed by our morphological studies of various parts of the gastrointestinal tract in this category of patients. From the above, it becomes clear not only the development of morphological disorders that take place in the conditions of rheumatological pathology and gastrointestinal pathology of an independent nature, but also the need to use in the correction of secondary gastrointestinal disorders in the Republic of Belarus as means that reduce the antigenic attack on the connective tissue stroma of the gastrointestinal tract, as well as agents that have a cytoprotective effect on the epithelial cells of this tract.

It is known that an important indicator that determines the ability of tissues to recover after their damage is the parameters characterizing the intensity of cell renewal processes: the degree of death and proliferation, as well as their ratio (B.K. Nurgaliyeva, G.A. Khamidulina, V.T. Ivashkin et al., 2005). If the process of cell death prevails over the process of proliferation, then cell "collapse" occurs - atrophy, and if, on the contrary, hyperplasia occurs (A.V. Kononov, S.I. Mozgovoy, M.A. Livzan and Dr. 2005). In the assessment of cell death processes, it is important to clarify the type of cell death: apoptosis or necrosis. Although both types of cell death ultimately lead to a decrease in the number of functioning cells, however, the death pathways chosen by cells are ambiguous in terms of cell renewal processes, in particular proliferation. Necrosis is the result of an unplanned event and occurs spontaneously, apoptosis is formed as a well-regulated, genetically determined process [2].

If the issue of cell renewal from the standpoint of apoptosis and proliferation in the conditions of pathology of the HD zone is currently sufficiently studied, the nature of these processes in the gastrointestinal tract in the conditions of rheumatological pathology remains unresolved, especially regarding the dependence on the duration of the course of RH and the intake of drugs, in particular, NSAIDs.

In connection with the above, in this work we studied the indicators of cell renewal (apoptosis, necrosis, proliferation, etc.), as well as genetic markers (p53, PCNA) of this

process in the stomach in the examined patients with RH (at the onset and in the conditions of a long-term course of the pathology) in a comparative aspect with patients with BU.

The results of studies in this direction indicate that in RB in the gastric mucosa there is an activation of epithelial apoptosis, which becomes more pronounced against the background of anti-inflammatory therapy (Fig. 1). At the same time, the balance between the processes of cell death and repair of gastric mucosa cells is disturbed due to the predominance of apoptosis over mitosis.

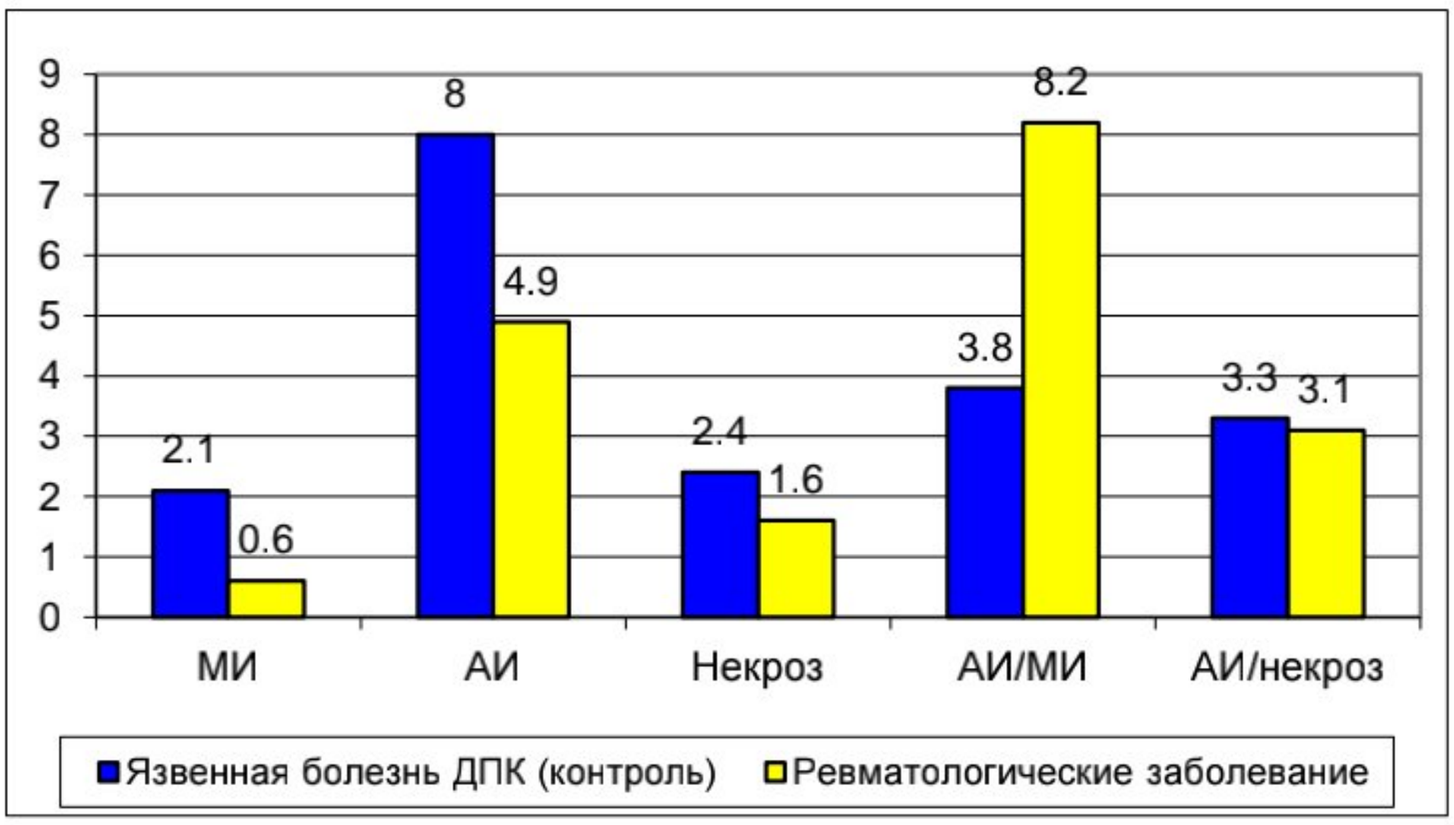

Fig.1. Some indicators of cellular renewal in the gastric mucosa in rheumatological patients

In general, disorders of cellular renewal processes in the gastric mucosa in RB are comparable to BU, as evidenced by shifts in the expression of genetic markers P-53 and PCNA (Fig. 2,3). With the long-term course of RH and the use of NSAIDs, disorders of cell renewal processes in the gastric mucosa become more pronounced than in patients with BU.

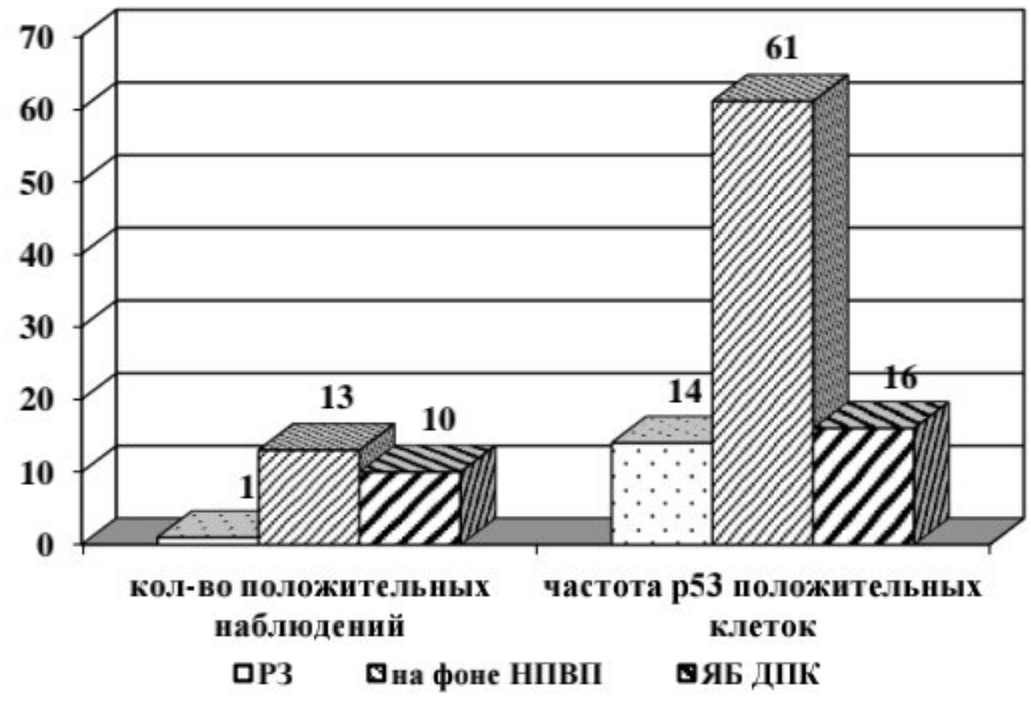

Fig.2. Expression of p53 protein in coolant in rheumatological patients

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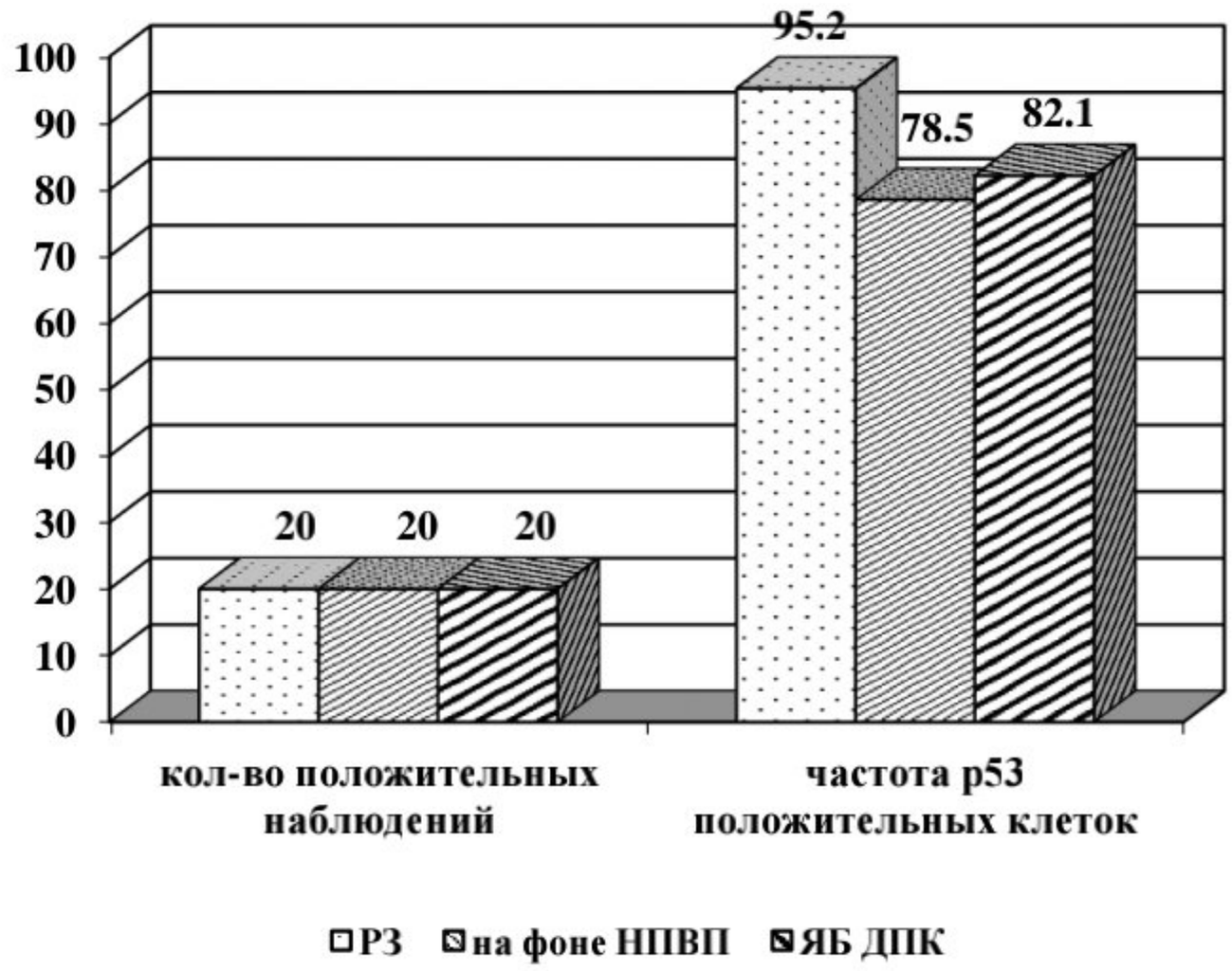

Fig.3. PCNA protein expression in coolant in rheumatological patients

Conclusion

Thus, the results of the studies allow us to conclude that RB has a lesion of the gastrointestinal tract, even before the use of drugs (NSAIDs), and on the part of all parts of the gastrointestinal tract. Gastrointestinal lesions in the Republic of Belarus are confirmed by clinical, functional, endoscopic, microbiological, structural and biochemical research methods. The severity of gastrointestinal damage in RB depends on the duration of the disease. In the onset of RH, there are certain shifts in the functional activity of the gastrointestinal tract, while the symptom complex on the part of the digestive tract is not identical to the symptom complex that takes place in BP DPC. A distinctive feature of gastrointestinal lesions at the onset of RH is the presence of frequent signs of involvement of the large intestine in the pathological process. If at the onset of the disease, clinical symptoms prevail over other signs, then with an increase in the duration of the medical history, clinical symptoms, on the contrary, give way to other manifestations of gastrointestinal damage. It is possible that in the mechanisms of increasing gastrointestinal symptoms in this category of patients, the priority role is played by drugs used in the treatment of RH and, first of all, NSAIDs.

In RB, there is a noticeable increase in the processes of cell death, due to the predominance of necrotic death over apoptotic death, and a sharp decrease in the proliferative activity of the gastric epithelium, which is confirmed by genetic markers of apoptosis and proliferation. These patterns are less pronounced than in gastric ulcers, especially at the onset of the disease.

Thus, the primary damage to the connective tissue structures of the gastrointestinal tract, on the one hand, and the cytodestructive effect of drugs used for the treatment of

RH, on the other hand, have a destabilizing effect on the parenchymal cells of the digestive tube, creating conditions for the occurrence of functional (at the onset) and organic changes in this system. These changes undoubtedly have a negative impact on the course of the underlying disease, aggravating its clinical manifestations and reducing the effectiveness of treatment.

Thus, the conducted studies indicate that there are clinical, biochemical, functional, and microbiological disorders of the gastrointestinal tract in the Republic of Belarus. These changes can be traced not only in patients with a certain duration of the course of RH, but also in the onset of the disease. In addition, they are not equally represented depending on the gastrointestinal tract and the duration of the disease. Drugs used for the treatment of rheumatological pathology, in particular NSAIDs, contribute to the aggravation of existing disorders of the digestive tube.

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