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**Specifics of vascular endothelium in patients with chronic inflammatory bowel diseases  
and different nutritional status**

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**Стан судинного ендотелію у пацієнтів з хронічними запальними захворюваннями  
кишечника з різним нутритивним статусом**

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**Состояние сосудистого эндотелия у пациентов с хроническими воспалительными  
заболеваниями кишечника с различным нутритивным статусом**

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## Summary

**Background.** Evaluation of endothelial function by non-invasive methods plays a major role in predicting the course of various diseases, the risk of complications and evaluation of treatment.

**Aim.** Evaluation of endothelial function in patients with chronic inflammatory bowel disease (IBD) according to their nutritional status by determining the specifics of the vascular endothelium in a sample with reactive hyperemia and the content of nitrogen oxide metabolites.

**Materials and methods.** 120 chronic IBD patients (81 patients with nonspecific ulcerative colitis (NUC) and 39 patients with Crohn's disease (CD)) depending on the anthropometric characteristics were divided into groups: I - reduced nutritional status (n = 70); II – normal nutritional status (n = 20); III - increased nutritional status (n = 30). In the blood serum of patients, the level of metabolites of nitric oxide (NOx) was determined according to Metelskaya technique. To assess endothelial function, endothelium-dependent vasodilation of the brachial artery was determined by a test with reactive hyperemia.

**Results.** On the basis of conducted studies, a significant decrease in the NOx content in the blood serum of patients was observed: 1.7-fold ( $p < 0.01$ ) in NUC patients and 1.7-fold ( $p < 0.001$ ) in CD patients. Reduction of the NOx content in the blood serum did not depend on the nutritional status of patients with chronic IBD. Violation of vascular endothelial function was found in 76.7% of patients: decreased endothelial function in 49.2% of patients, endothelial dysfunction in 27.5% of patients. Changes in vascular endothelial function have been found in 75.7% of Group I patients, 75% of Group II patients and 83.4% of Group III patients, mainly decreased endothelial function. **Conclusions.** It is shown that 71% of chronic IBD patients have a significant decrease in serum NOx, which does not depend on their nutritional status. Patients with NUC have more pronounced changes in the frequency of detected disorders and more pronounced increase in the diameter of the brachial artery, compared with CD patients. Reduced nutritional status was accompanied with the changes in vascular endothelial function in 75.4% of cases.

**Key words:** chronic inflammatory bowel diseases; vascular endothelium; Nitric oxide.

## Резюме

**Актуальність.** Оцінка ендотеліальної функції неінвазивними методами дослідження відіграє основну роль для прогнозування перебігу різних захворювань, ризику розвитку ускладнень та оцінки лікування. **Мета.** Оцінка ендотеліальної функції у пацієнтів з хронічними запальними захворюваннями кишечника (ХЗЗК) з різним нутритивним статусом шляхом визначення стану судинного ендотелію в пробі з реактивною гіперемією та вмісту метаболітів оксиду азоту в сироватці крові. **Матеріали та методи.** В дослідження було включено 120 пацієнтів з ХЗЗК (81 пацієнт з неспецифічним виразковим колітом (НВК) та 39 пацієнтів із хворобою Крона (ХК)), які в залежності від антропометричних характеристик були розподілені на групи: I – зі знизеним ( $n=70$ ); II – з нормальним ( $n=20$ ); III – з підвищеним нутритивним статусом ( $n=30$ ). У сироватці крові пацієнтів визначали рівень метаболітів оксиду азоту (NOx) за Метельською В.А. Для оцінки ендотеліальної функції використовували методику визначення ендотелій-залежної вазодилатації плечової артерії в пробі з реактивною гіперемією. **Результати.** На основі проведених досліджень встановлено вірогідне зниження вмісту NOx в сироватці крові пацієнтів з НВК в 1,7 разів ( $p<0,01$ ) та з ХК – в 1,9 разів ( $p<0,001$ ). Зниження вмісту NOx в сироватці крові не залежало від нутритивного статусу пацієнтів з ХЗЗК. Порушення функції судинного ендотелію виявлено у 76,7% пацієнтів: знизена функція ендотелію (ЗФЕ) визначалася у 49,2% пацієнтів, дисфункція ендотелію (ДФЕ) – у 27,5% пацієнтів. Виявлено зміни функції судинного ендотелію у 75,7% пацієнтів I групи, у 75% пацієнтів II групи та 83,4% пацієнтів III групи, переважно за рахунок зниження функції ендотелію. **Висновки.** Показано, що у 71% пацієнтів з ХЗЗК відбувається вірогідне зниження вмісту NOx в сироватці крові, що не залежить від їх нутритивного статусу. У пацієнтів з НВК спостерігалися більш виражені зміни за частотою виявлених порушень та показником відсотку приросту діаметру плечової артерії, в порівнянні з ХК. При знизеному нутритивному статусі зміни функції судинного ендотелію спостерігались у 75,4 % випадків.

**Ключові слова:** хронічні запальні захворювання кишечника; судинний ендотелій; оксид азоту.

## Резюме

**Актуальность.** Оценка эндотелиальной функции неинвазивными методами исследования играет основную роль для прогнозирования течения различных заболеваний, риска развития осложнений и оценки лечения. **Цель.** Оценка эндотелиальной функции у пациентов с хроническими воспалительными заболеваниями кишечника (ХВЗК) с различным нутритивным статусом путем определения состояния сосудистого эндотелия в пробе с реактивной гиперемией и содержания метаболитов оксида азота. **Материалы и методы.** В исследование было включено 120 пациентов с ХВЗК (81 пациент с неспецифическим язвенным колитом (НЯК) и 39 пациентов с болезнью Крона (БК)), которые в зависимости от антропометрических характеристик были разделены на группы: I – со сниженным (n=70); II – с нормальным (n=20); III – с повышенным нутритивным статусом (n=30). В сыворотке крови пациентов определяли уровень метаболитов оксида азота (NOx) по Метельской В.А. Для оценки эндотелиальной функции использовали методику определения эндотелий-зависимой вазодилатации плечевой артерии в пробе с реактивной гиперемией. **Результаты.** На основе проведенных исследований установлено достоверное снижение содержания NOx в сыворотке крови пациентов с НЯК в 1,7 раза ( $p<0,01$ ) и с БК – в 1,9 раз ( $p<0,001$ ). Снижение содержания NOx в сыворотке крови не зависело от нутритивного статуса пациентов с ХВЗК. Нарушение функции сосудистого эндотелия обнаружено у 76,7% пациентов: сниженная функция эндотелия (СФЭ) определялась в 49,2% пациентов, дисфункция эндотелия (ДФЭ) – в 27,5% пациентов. Выявлены изменения функции сосудистого эндотелия в 75,7% пациентов I группы, у 75% пациентов II группы и 83,4% пациентов III группы, преимущественно за счет снижения функции эндотелия. **Выводы.** Показано, что у 71% пациентов с ХВЗК происходит достоверное снижение содержания NOx в сыворотке крови, что не зависит от их нутритивного статуса. У пациентов с НЯК наблюдались более выраженные изменения по частоте выявленных нарушений и показателю процента прироста диаметра плечевой артерии, по сравнению с БК. При сниженном нутритивном статусе изменения функции сосудистого эндотелия наблюдались в 75,4% случаев.

**Ключевые слова:** хронические воспалительные заболевания кишечника; сосудистый эндотелий; оксид азота.

## **Introduction**

Inflammatory bowel diseases, including nonspecific ulcerative colitis (NUC) and Crohn's disease (CD), lead to chronic inflammation, mainly affecting the gastrointestinal tract. This pathology requires surgical intervention in 16% and 47% of NUC and CD patients, respectively, every 10 years after the onset of the disease. As a result, patients with chronic inflammatory bowel disease (IBD) experience a significant decline in quality of life, when compared to healthy people of the same age [1]. According to recent epidemiological studies, the annual incidence of NUC in Europe is 10.4 cases, and CD – 5.6 cases per 100,000 population with the largest gradient observed in Scandinavia (24.5 and 9.2 cases per 100,000 respectively) In Europe, more than 2.2 million people suffer from these diseases. NUC is found somewhat more often in men than in women – 1.39:1, whereas with CD the opposite ratio is determined – 1: 1.12 [2].

In Ukraine in 2015 diseases of intestinal localization took 3.7% in the structure of the digestive diseases, with a predominance of NUC over CD (4.4: 1). Aside from that, it is important to note that the absolute number of CD among the working-age population has increased [3].

Endothelial dysfunction is a multifaceted process, one of the earliest manifestations of which is a violation of the bioavailability of nitric oxide (NO) under the influence of many pathological factors [4]. NO belongs to the most important biological mediators in the human body and participates in the regulation of intra- and intercellular processes in various organs and tissues. Its serum content depends on many factors: the activity of NO-synthase (NOS), the structural and functional state of the endothelium, the concentration of free radicals, exo- and endotoxins, inflammatory mediators, and others. [5]. Oxidative stress is the cause of inactivation of nitrites and nitrates and, accordingly, causes a decrease in the concentration of NO in the tissues, preventing vasodilation. Insufficient production of endothelial NO is accompanied by increased tonus and vascular spasm, increased vascular permeability for proteins and lipoproteins, accelerated proliferation of smooth muscle cells, expression of adhesive molecules on the surface of endothelial cells without interference, increased thrombus formation [6]. Various pathological processes in the body are accompanied by a violation of the function of the vascular endothelium, which may lead to the progression of vascular insufficiency. The evaluation of endothelial function by non-invasive methods plays a major role in predicting the course of the disease, the risk of developing complications, and evaluation of the treatment [7, 8].

Methods of studying the endothelium function can be divided into two large groups: I - invasive techniques, in which instrumental, clinical and laboratory methods of research are

used; II - non-invasive options, based on the methods of functional diagnostics. The "golden standard" for the study of endothelial function is currently not established yet [9]. Over the past 25 years, many methodological approaches have been developed to evaluate the function of endothelium in humans [10]. Possibilities of measuring indicators that characterize the endothelial function are widely used in scientific research. However, their use as a clinical tool in daily medical practice is still not very common [11]. The aim of the present work was to assess the endothelial function in patients with chronic inflammatory bowel disease (IBD) according to their nutritional status by determining the specifics of the vascular endothelium in a sample with reactive hyperemia and the content of nitrogen oxide metabolites.

### **Materials and methods**

120 chronic IBD patients (81 patients with nonspecific ulcerative colitis (NUC) and 39 patients with Crohn's disease (CD)) was observed in the Department of Bowel Diseases, the Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, during the period from 2014 to 2016; among them 45.8% women, 54.2% men with the mean age ( $38.13 \pm 1.08$ ) years. Depending on the anthropometric characteristics, all patients were divided into three groups: I – with a reduced nutritional status ( $n = 70$ ); II - with normal nutritional status ( $n = 20$ ); III – with increased nutritional status ( $n = 30$ ).

Patients' blood serum was used to determine the level of nitrogen oxide metabolites (NO<sub>x</sub>) according to Metelskaya technique, where vanadium chloride (Sigma-Aldrich) was used as a reducing agent for nitrates [12]. The control group included 20 practically healthy individuals, and the NO<sub>x</sub> content in serum for them was (25–58)  $\mu\text{mol/L}$ .

Method for determining endothelium-dependent vasodilatation of the brachial artery in a reactive hyperemia test was used to evaluate the endothelial function [13]. The method is based on determining the growth of the diameter of the brachial artery (dBA) in response to mechanical stimulation (transient occlusion of the shoulder as a result of compression of the sphygmomanometer cuff above the location of the vessel). In normal circumstances, post-occlusive blood flow is characterized by a peak increase in volume and linear velocity that occurs in the first 30 seconds after the removal of occlusion, with a gradual decrease in speed. In response to an increase in blood flow, there is a temporary increase in the shear stress on the endothelium, which, in turn, is accompanied by the release of substances that have vasodilatational activity, which causes an increase in dBA. Toshiba Xario ultrasound scanner with a 7.5 MHz multifrequency linear sensor was used to access the changes in dBA (Figure 1).

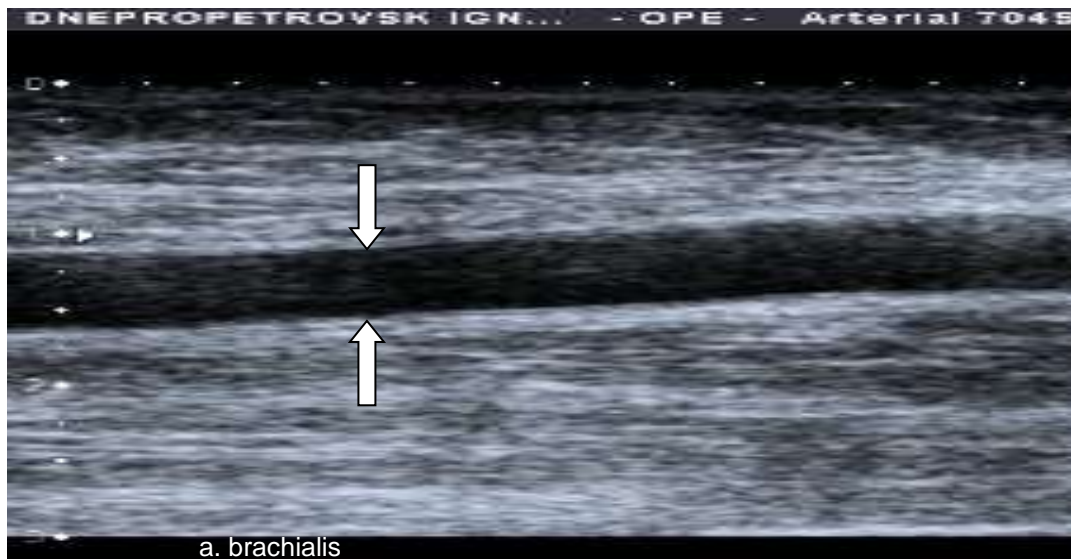


Figure 1 - Sonoelostogram of the brachial artery in patients with chronic IBD.

Endothelial function index (EFI) (response to blood flow increase) was calculated as the difference between dBA after decompression and baseline, expressed as a percentage:

$$EFI = \frac{(\text{dBA after compression} - \text{dBA before compression})}{(\text{dBA initial})} \times 100\%$$

An increase in dBA by more than 20% indicated a normal function of the vascular endothelium (NEF), by 10–20% decreased endothelium function (DEF), by less than 10% – endothelial dysfunction (EDF).

The control group included 20 healthy individuals, of representative age and sex.

Descriptive statistics were used for statistical analysis of data; the comparison of the mean values of variables was carried out using parametric methods (Student's t-criterion) for the normal distribution of the data expressed in the interval scale.

The correspondence of the characteristics distribution to the normal distribution law was verified using the Shapiro-Wilk method. In other cases, a non-parametric method was used (Mann-Whitney U-criterion).

To compare the particle distribution of two or more variables, the  $\chi^2$  test was used. Correlation analysis was performed by Pearson method (for data expressed on interval scale) and Spearman (for data not expressed on interval scales).

All calculations were performed in SPSS 9.0 for Windows [14].

## Results and discussion

The analysis showed a significant decrease of NO<sub>x</sub> content in patients with NUC. The mean NO<sub>x</sub> values were significantly different from the control group and were reduced: in the general group of patients 1.7-fold ( $23.83 \pm 1.15$  versus  $41.65 \pm 5.55$   $\mu\text{mol/L}$ ,  $p < 0.01$ ), in NUC patients also 1.7-fold ( $24.74 \pm 1.47$  versus  $41.65 \pm 5.55$   $\mu\text{mol/L}$ ,  $p < 0.01$ ) and in CD patients 1.9-fold ( $21.70 \pm 1,70$  versus  $41.65 \pm 5.55$   $\mu\text{mol/L}$ ,  $p < 0.001$ ). An intragroup analysis showed that in the NUC and CD groups, the vast majority of patients had a lower NO<sub>x</sub> content: 72.0% ( $p < 0.001$ ) and 68.8% ( $p < 0.001$ ), respectively, as compared to control (Figure 2).

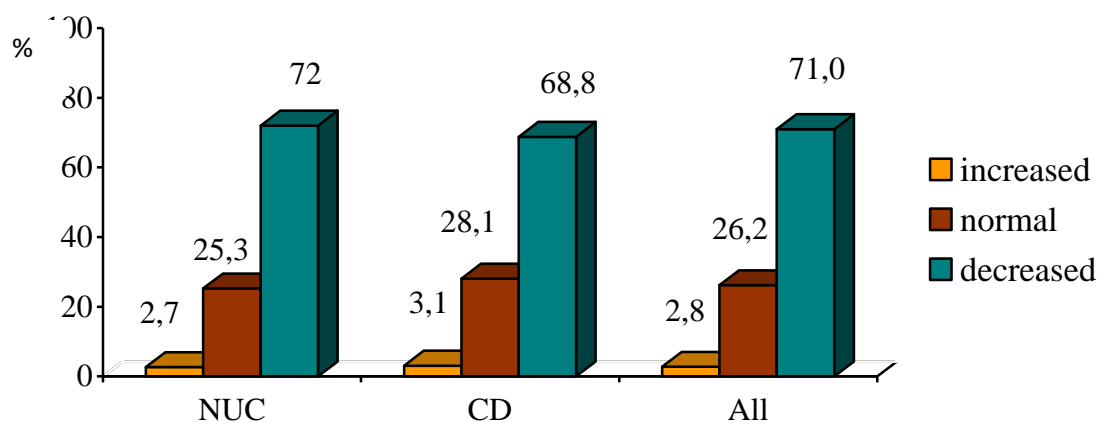


Figure 2 - Percentage of chronic IBD patients according to their NO<sub>x</sub> serum levels.

The content of NO<sub>x</sub> in blood serum of patients with different nutritional status varied as follows: 1.8-fold decreased in group I ( $23.79 \pm 1.62$  versus  $41.65 \pm 5.55$   $\mu\text{mol/L}$ ,  $p < 0.01$ ) – 1,9-fold decreased in group II ( $22,12 \pm 2,32$  versus  $41,65 \pm 5,55$   $\mu\text{mol/L}$ ,  $p < 0,01$ ), and 1,7-fold decreased in group III ( $25,12 \pm 2.26$  versus  $41.65 \pm 5.55$   $\mu\text{mol/L}$ ,  $p < 0.01$ ). Thus, a significant decrease of serum NO<sub>x</sub> levels in chronic IBD patients is shown, regardless of nutritional status. Such a decrease in the synthesis of NO occurs more often with prolonged and severe influence of adverse factors and corresponds to the stage of exhaustion. This may lead to further decrease in protective functions of the vascular endothelium.

Taking into account the detected decrease in serum NO<sub>x</sub> content, it was decided to investigate the state of the vascular endothelium in chronic IBD patients.

Results of endothelium dependent vasodilatation of the brachial artery by reactive hyperemia test in the examined patients are presented in Table 1.

Table 1 – Indices of endothelium dependent vasodilatation determined by the reactive hyperemia test in chronic IBD patients.

Patient groups	NEF (n=28)	DEF (n=59)	EDF (n=33)
	average increase in dBA,%		
All (n=120)	27,40±1,05	14,94±0,71*	7,38±1,77#
NUC (n=81)	27,08±1,50	15,12±0,77*	8,51±1,51#
CD (n=39)	25,86±1,02	14,45±0,47*	7,72±1,44#

Notes: \* –  $p < 0,05$  – statistically significant difference between patients with normal and reduced function of the endothelium; # –  $p < 0,05$  – statistically significant difference between patients with endothelial dysfunction and decreased endothelial function.

According to the presented data, the changes of vascular endothelium was detected in 76.7% of the examined patients. Patients with DEF prevailed in the structure of changes (49.2%), patients with EDF were present twice less frequently (27.5%). The mean values of the dBA increase rate were lower than normal values and corresponded to DEF (Table 2, Fig. 3).

Table 2 - Results of reactive hyperemia test in chronic IBD patients.

Patient groups	dBA before compression	dBA after compression	% dBA increase, mm
All (n=120)	3,32±0,62	3,83±0,70	15,83±0,18
NUC (n=81)	3,40±0,59	3,70±0,71	15,29±0,49
CD (n=39)	3,15±0,59	3,70±0,71	16,94±0,47

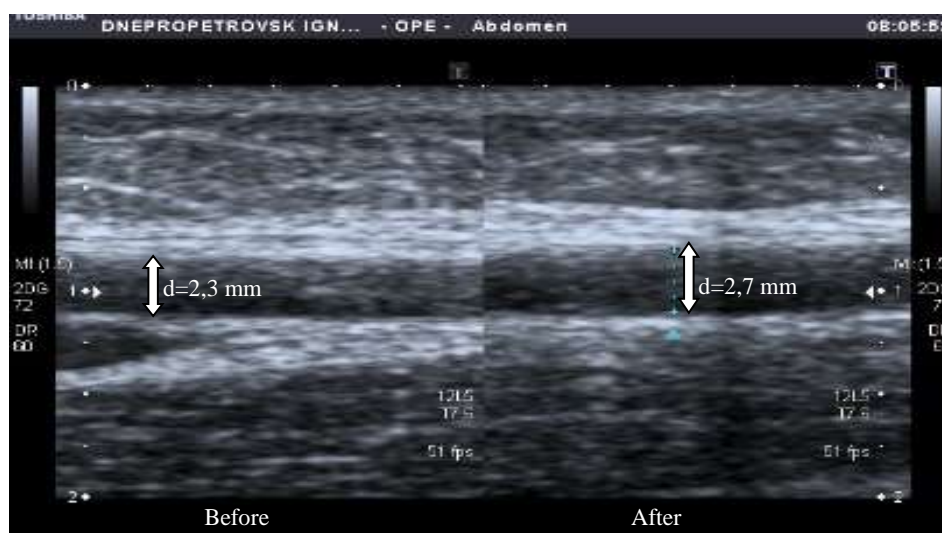


Figure 3 - Sonoelostogram of the brachial artery (diameter before and after compression) in chronic IBD patients with reduced function of the endothelium.

Analysis of nosologies showed that changes in vascular endothelium were detected in 62 (76.5%) patients with NUC and in 31 (79.4%) CD patients, mainly due to decreased function of the endothelium (Fig. 4). There was a positive correlation between the percentage

of dBA increase and the age of patients ( $r = 0.22$ ,  $p = 0.015$ ), duration of the disease ( $r = 0.21$ ,  $p = 0.22$ ). In the group of CD patients, an additional correlation link between the percentage of dBA increase and the erythrocyte sedimentation rate has been found ( $r = 0.35$ ,  $p = 0.03$ ) (data are not given).

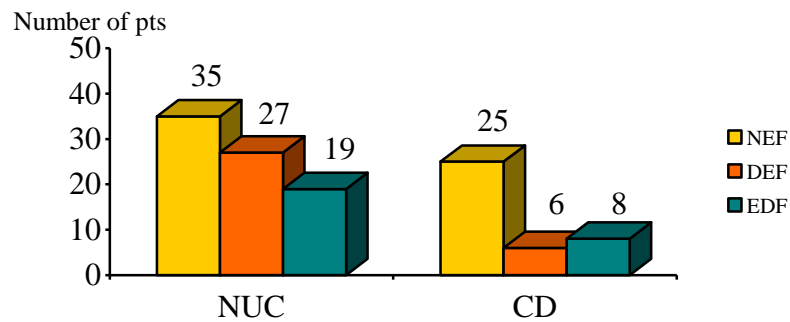


Figure 4 - Chronic IBD patients, distributed by the vascular endothelium function.

In NUC patients, DEF was detected in 43.2% of cases, and DFE in 33.3% of cases, and in CD patients DEF was detected in 64.1% of cases, EDF in 15.4% of cases. The statistically significant differences between nosological groups were not found.

We further investigated the function of vascular endothelium, depending on patients' nutritional status. The results of endothelium dependent vasodilatation of the brachial artery determined by the reactive hyperemia test showed that the percentage of dBA increase was smaller both in Group I and Group II patients compared to controls (Table 3).

Table 3 – Results of reactive hyperemia test in chronic IBD patients depending on their nutritional status

Index	Group I (n=70)	Group II (n=20)	Group III (n=30)
dBA before	3,36±0,60	3,29±0,66	3,25±0,65
dBA after	3,93±0,70	3,72±0,71	3,68±0,67
% dBA increase, mm	17,21±0,76	14,45±0,45*	13,53±0,63**

Notes: \* –  $p < 0,05$  – statistically significant difference between Group I and Group II patients; # –  $p < 0,05$  – statistically significant difference between Group I and Group III patients.

Group III patients were characterized by the lowest average percentages of dBA increase. In addition, in Group II patients dPA increase was also lower than in the control group. A more detailed analysis revealed changes in the vascular endothelium in 53 (75.7%) Group I patients, in 15 (75.0%) Group II patients and in 25 (83.4%) Group III patients, mainly due to decreased endothelial function.

Thus, a study of the functional status of the vascular endothelium by the reactive hyperemia test with ultrasound revealed a disturbance in 76.7% of the examined chronic IBD patients with a predominance of DEF in 50.0% and EDF in 26.7% of cases. More pronounced changes both in the frequency of violations, and in the percentage of dBA increase was found in the NUC patients, compared to the CD patients. In patients with nutritional deficiency, changes in the vascular endothelium were observed in 75.4% of cases, while the endothelium-dependent vasodilatation of the brachial artery was significantly higher when compared to the patients with normal nutritional status: ( $17.21 \pm 0.76$  vs.  $14.45 \pm 0.45$  mm), respectively.

### **Conclusions**

1. It has been shown that 71% of chronic IBD patients (72% of patients with NUC and 68.8% of CD patients) demonstrate statistically significant decrease in serum NOx content, which may lead to the violation of the protective functions of the vascular endothelium, which in turn confirms inadequate activation of protective antioxidant system and leads to the disease exacerbation and its chronic course. The probable decrease in serum NOx content in chronic IBD patients did not depend on their nutritional status.

2. Dysfunction of the vascular endothelium were detected in 76.7% of the examined patients with predominance of DEF (in 50.0% of patients). Patients with NUC had more pronounced changes in the frequency of identified violations and percentage of dBA increase, compared with CD. Changes in the vascular endothelium were observed in 75.4% of the reduced nutritional status cases, while the indexes of endothelium-dependent vasodilatation of the brachial artery were significantly higher compared to patients with normal nutritional status ( $p < 0.05$ ).

**Conflict of interest.** The authors declare no conflict of interest.

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