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Fatty Acids of Erythrocyte Membranes and Blood Serum as Possible Predictors of Exacerbation in Patients with Inflammatory Bowel Diseases

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Aim: to study the levels of fatty acids in the membranes of erythrocytes and blood serum in patients with inflammatory bowel diseases (IBD) examined over time, as possible predictors of exacerbation of the disease.
Materials and methods. Over a period of 6–12 months, 24 patients (mean age — 38.2 ± 4.4 years) with IBD with of moderate and mild severity of the disease were examined, of which 10 patients had ulcerative colitis, 10 — Crohn's disease, 4 — unclassified colitis: the first examination was in the acute stage, the second was in the remission stage. In 48 additionally examined patients with IBD in remission (25 patients with ulcerative colitis, 15 — with Crohn's disease, 8 — with unclassified colitis), the course of the disease was monitored over the next 12 months. The comparison group included 53 people comparable to the main groups in age. The study of the composition of fatty acids (FAs) in the membranes of erythrocytes and blood serum was carried out using a gas chromatograph mass spectrometry system based on three quadrupoles Agilent 7000B (Agilent Technologies Inc., USA).
Results. In the acute stage, patients with IBD have a higher total content of saturated fatty acids (SFAs) in erythrocyte membranes compared to the control group ($p = 0.006$), and, on the contrary, lower levels of unsaturated fatty acids (UFAs) ($p = 0.005$), mainly due to polyunsaturated FAs (PUFAs) ($p = 0.026$), namely omega-6 PUFAs ($p = 0.011$). Remission of IBD is associated with an increase in the level of a number of SFAs in the blood serum — margaric C17:0 ($p = 0.024$), arachidic acid (C20:0) — in erythrocyte membranes and serum ($p = 0.0001$ and $p = 0.019$, respectively), with a decrease in the total content of monounsaturated FAs in erythrocyte membranes ($p = 0.022$), an increase in the total concentration of PUFAs due to both omega-3 PUFAs ($p = 0.0008$) and omega-6 PUFAs ($p = 0.033$) in erythrocyte membranes compared with a group of healthy individuals.
The exacerbation stage in patients with IBD examined over time is associated with higher levels of stearic FA C18:0 ($p = 0.005$), SFA/UFA ($p = 0.034$) and SFA/PUFA ($p = 0.039$) ratios in erythrocyte membranes, serum level of arachidic FA C20:0 ($p = 0.008$), and, on the contrary, lower content of UFAs in erythrocyte membranes — eicosapentaenoic C20:5n-3 ($p = 0.0023$), eicosadienoic C20:2n-6 ($p = 0.0027$), hexadecadienoic C16:2n-6 ($p = 0.006$), docosatetraenoic C22:4n-6 ($p = 0.008$) and alpha-linolenic C18:3n-3 ($p = 0.039$).
A combined "panel" of fatty acids, including the levels of C20:2n-6, C18:0 in erythrocyte membranes and the content of C20:0 in blood serum, provided an AUC of 0.683 (95 % CI: 0.500–0.844), sensitivity 91.4 %, specificity 68.3 %.
Levels of C20:5n-3, C20:2n-6, C18:0, C16:2n-6, C22:4n-6, C18:3n-3 fatty acids, SFA/UFA and SFA/PUFA ratios in erythrocyte membranes and content C20:0 in blood serum, used as biomarkers — predictors of the development of exacerbation in patients with IBD who were in remission, predicted the development of exacerbation of IBD after 2–4 months in the case of maximally changed levels of FAs, after 6–8 months — with moderately changed levels FAs, maintaining remission for 12 months — with minimally changed FAs levels.
Conclusion. Fatty acids of erythrocyte membranes and blood serum should be considered as promising markers for further studies related to the diagnosis and prediction of exacerbation in IBD.
Keywords: inflammatory bowel diseases, prediction of exacerbation, fatty acids, erythrocyte membranes, blood serum
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Жирные кислоты мембран эритроцитов и сыворотки крови как возможные предикторы развития обострения у пациентов с воспалительными заболеваниями кишечника

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Цель исследования: изучить уровни жирных кислот мембран эритроцитов и сыворотки крови у пациентов с воспалительными заболеваниями кишечника (ВЗК), обследованных в динамике, в качестве возможных предикторов обострения заболевания.

Материалы и методы. В динамике в течение 6–12 месяцев обследованы 24 пациента (средний возраст — 38,2 ± 4,4 года) с ВЗК средней и легкой степени тяжести заболевания, из них 10 пациентов — с язвенным колитом, 10 — с болезнью Крона, 4 — с неклассифицируемым колитом: первое обследование — в стадии обострения, второе — в стадии ремиссии. У 48 дополнительно обследованных пациентов с ВЗК в стадии ремиссии (25 пациентов с язвенным колитом, 15 — с болезнью Крона, 8 — с неклассифицируемым колитом) проведен мониторинг течения заболевания в течение последующих 12 месяцев. Группу сравнения составили 53 человека, сопоставимые по возрасту с пациентами основных групп. Исследование состава жирных кислот мембран эритроцитов и сыворотки крови проведено с помощью системы газовой хромато-масс-спектрометрии на основе трех квадруполей Agilent 7000B («Agilent Technologies Inc.», США).

Результаты. В стадии обострения у пациентов с ВЗК выше суммарное содержание насыщенных жирных кислот (НЖК) в мембранах эритроцитов по сравнению с группой контроля (p = 0,006) и, напротив, ниже содержание ненасыщенных жирных кислот (ННЖК) (p = 0,005), преимущественно за счет полиненасыщенных жирных кислот (ПНЖК) (p = 0,026), а именно — омега-6 ПНЖК (p = 0,011). Ремиссия ВЗК ассоциирована с повышением уровня ряда НЖК в сыворотке крови — маргариновой C17:0 (p = 0,024), арахиновой C20:0 — в мембранах эритроцитов и сыворотке (p = 0,0001 и p = 0,019 соответственно); со снижением суммарного содержания мононенасыщенных жирных кислот в мембранах эритроцитов (p = 0,022); повышением суммарной концентрации ПНЖК, как за счет омега-3 ПНЖК (p = 0,0008), так и омега-6 ПНЖК (p = 0,033), в мембранах эритроцитов по сравнению с группой здоровых лиц.

Стадия обострения у пациентов с ВЗК, обследованных в динамике, ассоциирована с более высокими уровнями стеариновой жирной кислоты C18:0 (p = 0,005), отношений НЖК/ННЖК (p = 0,034), НЖК/ПНЖК (p = 0,039) в мембранах эритроцитов, сывороточным уровнем арахиновой жирной кислоты C20:0 (p = 0,008) и, напротив, более низким содержанием ННЖК в мембранах эритроцитов — эйкозапентаеновой C20:5n-3 (p = 0,0023), эйкозадиеновой C20:2n-6 (p = 0,0027), гексадекадиеновой C16:2n-6 (p = 0,006), докозатетраеновой C22:4n-6 (p = 0,008) и альфа-линоленовой C18:3n-3 (p = 0,039).

Комбинированная «панель» жирных кислот, включающая уровни C20:2n-6, C18:0 в мембранах эритроцитов и содержание C20:0 в сыворотке крови, обеспечила AUC 0,683 (95 % ДИ: 0,500–0,844), чувствительность 91,4 % и специфичность 68,3 %.

Уровни жирных кислот C20:5n-3, C20:2n-6, C18:0, C16:2n-6, C22:4n-6, C18:3n-3, соотношений НЖК/ННЖК, НЖК/ПНЖК в мембранах эритроцитов и содержание C20:0 в сыворотке крови, использованные как биомаркеры — предикторы развития обострения у пациентов с ВЗК, находившихся в стадии ремиссии, предсказали развитие обострения ВЗК через 2–4 месяца в случае максимально измененных уровней жирных кислот, через 6–8 месяцев — при умеренно измененных уровнях жирных кислот, сохранение ремиссии в течение 12 месяцев — при минимально измененных уровнях жирных кислот.

Заключение. Жирные кислоты мембран эритроцитов и сыворотки крови следует рассматривать как перспективные маркеры для дальнейших исследований, связанных с диагностикой и предикцией развития обострения при ВЗК.

Ключевые слова: воспалительные заболевания кишечника, предикция обострения, жирные кислоты, мембраны эритроцитов, сыворотка крови

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Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, are characterized by recurrent and remitting courses. The aim of therapy is to both induce and maintain persistent remission and prevent progression of pathologies. Outbreaks of activity of the disease occur randomly and are mostly unpredictable, and the constant inflammatory background negatively affects the patient's physical and psychological well-being, social activity and ability to work. Despite effective drug therapy that can guarantee clinical remission, some degree of subclinical inflammation may persist in the intestinal mucosa, increasing the risk of 'symptomatic' relapse when the inflammatory process reaches critical intensity [1].

The identification of objective markers capable of detecting such subclinical inflammation may represent an important step forward in clinical practice, allowing the gastroenterologist to select patients and plan individualized treatment. When verifying the diagnosis of IBD in clinical practice, a combination of case history, clinical symptoms, laboratory, radiological, endoscopy and histological examination of tissue samples are considered to assess disease activity and make treatment decisions [2]. None of the proposed markers are reliable in isolation as a predictor of the development of an active process in IBD [3]. To improve predictive ability, "diagnostic panels" integrating clinical and biological prognostic markers with the establishment of prognostic scores are being developed [4, 5].

From the point of view of potential biomarkers, fatty acids, which play a variety of roles in IBD, ranging from pro- and anti-inflammatory and immunoregulatory functions to modulation of gut microbiota and maintenance of correct functioning of the intestinal barrier, are promising [6].

The aim of the work was to study the levels of fatty acids of erythrocyte membranes and blood serum in patients with inflammatory bowel diseases examined in dynamics as possible predictors of disease exacerbation.

Material and methods

The study included 24 patients (13 women, 11 men) with IBD (mean age — 38.2 ± 4.4 years) who were examined in detail in the active stage before therapy and in the remission stage. Ten patients had ulcerative colitis (UC), 10 — had Crohn's disease (CD), and four had unclassifiable colitis (UCC). The diagnosis of IBD was established in accordance with the provisions of the Russian clinical guidelines for UC and CD [7, 8]. All patients had affected colon, mostly had a recurrent course of ICD, and the disease duration was 5.2 ± 3.7 years. 70.8 % were diagnosed with moderate severity of the disease, and 29.2 % with mild severity. During the period of exacerbation, clinical and endoscopic activity of moderate degree prevailed. The predominant part of patients with UC and NCC (n = 10, 41.7 %) had average severity of the present attack according to Meyo index (6–9 points), the remaining four persons (16.7 %) were diagnosed with mild attack (3–5 points). According to the Best's index values of 178.2 ± 29.1 points in patients with CD, the activity of the present attack corresponded to mild.

In the predominant number of patients (n = 16, 66.7 %) anaemia of various genesis was diagnosed in the active stage of the disease, arthralgia was of concern (n = 10, 41.7 %), liver steatosis and steatohepatitis were detected in 5 patients (20.8 %).

The second study of fatty acid levels of erythrocyte membranes, blood serum was performed in 6–12 months in remission stage, which was

confirmed by Meyo index in UC and Best's index in CD. Patients were treated with corticosteroids, aminosalicylates, immunomodulators, etc., according to Russian standards.

To test the predictive capabilities of erythrocyte parameters, 48 patients (26 women, 22 men) with IBD in clinical and endoscopic remission (mean age — 39.5 ± 4.9 years), which lasted from 6 to 12 months, were additionally examined. Of them 25 patients had UC, 15 — CD, 8 — NCC; 28 (58.3 %) people had a chronic recurrent course of the disease of moderate severity, 20 (41.7 %) patients — a mild one. At the time of examination, the inactive stage of the disease was confirmed by clinical data, endoscopy, biochemistry and fecal markers. The course of the disease (remission persistence, exacerbation development) in this group was monitored during the following year.

The formed comparison group included 53 people (28 women and 25 men; mean age — 43.3 ± 11.7 years), examined for preventive purposes, without bad habits, leading a healthy lifestyle, without manifesting diseases of therapeutic profile.

The concentration of fatty acids of erythrocyte membranes and blood serum, as well as the total concentrations of saturated, unsaturated, polyunsaturated, omega-3 PUFA, omega-6 PUFA, and their ratios, were estimated using gas chromatography/mass spectrometry (based on three Agilent 7000B quadrupoles (Agilent Technologies Inc., USA)). The fatty acid content was expressed as relative percentages. A detailed description of sample preparation, procedure for determination of fatty acid levels is given in the work [9]. The statistical analysis of the results obtained was performed using the SPSS program, ver. 17 (SPSS Inc., USA). Kolmogorov — Smirnov method was used. In the absence of normal distribution, medians (*Me*) were calculated with the indication of interquartile range (25th and 75th percentiles). The reliability of the difference between the indicators was assessed by the nonparametric Mann — Whitney test. The critical level of significance of the null hypothesis (p) was taken as 0.05. To determine the levels of fatty acids as potential predictors of exacerbation, the values of the indicators were normalized. Partial least-squares discriminant analysis (PLS DA) was used to determine the differences between the levels of fatty acids. Paired t-test (comparison of fatty acid levels of the same patient in the stage of exacerbation and remission) and Volcano plot method assessed the content of fatty acids as markers of exacerbation of the underlying disease. K-means clustering was used to measure the predictive power of the identified list of fatty acids. The system of machine learning methods — Random Forest with MATLAB software (R2019a, MathWorks, USA), R programming language with the use of standard libraries of training classifications and sets of statistical tools [10] was used in this work. ROC-analysis was used to assess the diagnostic accuracy of indicators.

The work was approved by the Biomedical Ethics Committee of the Research Institute of Therapy and Preventive Medicine — Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (protocol No. 120, December 17, 2018). All people included in the study signed informed consent for participation.

Results

At the first stage, the content of different classes of fatty acids (FAs) was analyzed in patients with IBD and in the comparison group. During the exacerbation of the disease, higher total saturated fatty acid (SFA) content in erythrocyte membranes (palmitic C16:0, stearic C18:0, arachidic C20:0) and in serum (p = 0.0000006–0.05) was observed in patients with IBD compared to healthy individuals. Concentrations of two SFAs in erythrocyte membranes tended to decrease in exacerbation of the disease — pentadecane C15:0 (p = 0.075) and margaric C17:0 (p = 0.052). Beyond the exacerbation, higher than in the control content of margaric (C17:0) FA in serum (p = 0.024), arachidic FA (C20:0) — in erythrocyte membranes (p = 0.0001) and serum (p = 0.019) was observed, and also lower level of C18:0 in serum (p = 0.05) and trend to decrease of serum total FA content was revealed.

Lower total levels of monounsaturated FAs were observed in erythrocyte membranes (p = 0.001) and serum (p = 0.02) during exacerbation of the underlying disease compared to the control group. The content of individual monounsaturated acids in erythrocyte membranes was statistically significantly lower or tended to be lower in active IBD: C16:1;7 (p = 0.079), C16:1;9 (p = 0.001), C18:1;c9 (p = 0.011), C18:1;t9 (p = 0.018). The remission stage of IBD was also found to be associated with lower levels of total monounsaturated FAs (p = 0.022), more due to C16:1;9 (p = 0.0001), partly — due to C16:1;7 (p = 0.068).

Erythrocyte membranes in patients with acute IBD were characterized by a lower total unsaturated fatty acid (UFA) content (p = 0.005), to a greater extent due to reduced levels of polyunsaturated FAs (PUFAs) (p = 0.02), especially omega-6 PUFAs (p = 0.01) compared to the control group. The ratios of SFA/UFA and SFA/PUFA were higher in the active phase of IBD both in

erythrocyte membranes ($p = 0.017$ and $p = 0.041$, respectively) and in serum ($p = 0.03$ and $p = 0.02$, respectively). In exacerbation of IBD, lower levels of linoleic acid C18:2n-6 in erythrocyte membranes were observed than in healthy individuals ($p = 0.0009$). In contrast, serum content of C20:2n-6 and C22:4n-6 was higher in active IBD than in controls ($p = 0.051$ and $p = 0.027$, respectively). Of omega-3 PUFAs, only the serum level of C22:5n-3 was higher in patients with acute IBD ($p = 0.05$) than in healthy subjects, while the omega-6 PUFA/omega-3 PUFA ratio was lower ($p = 0.03$).

In the remission stage of IBD, the total PUFA concentration was higher in the erythrocyte membranes of patients with IBD ($p = 0.005$) than in the comparison group, both due to omega-3 PUFA ($p = 0.0008$) (including the sum of

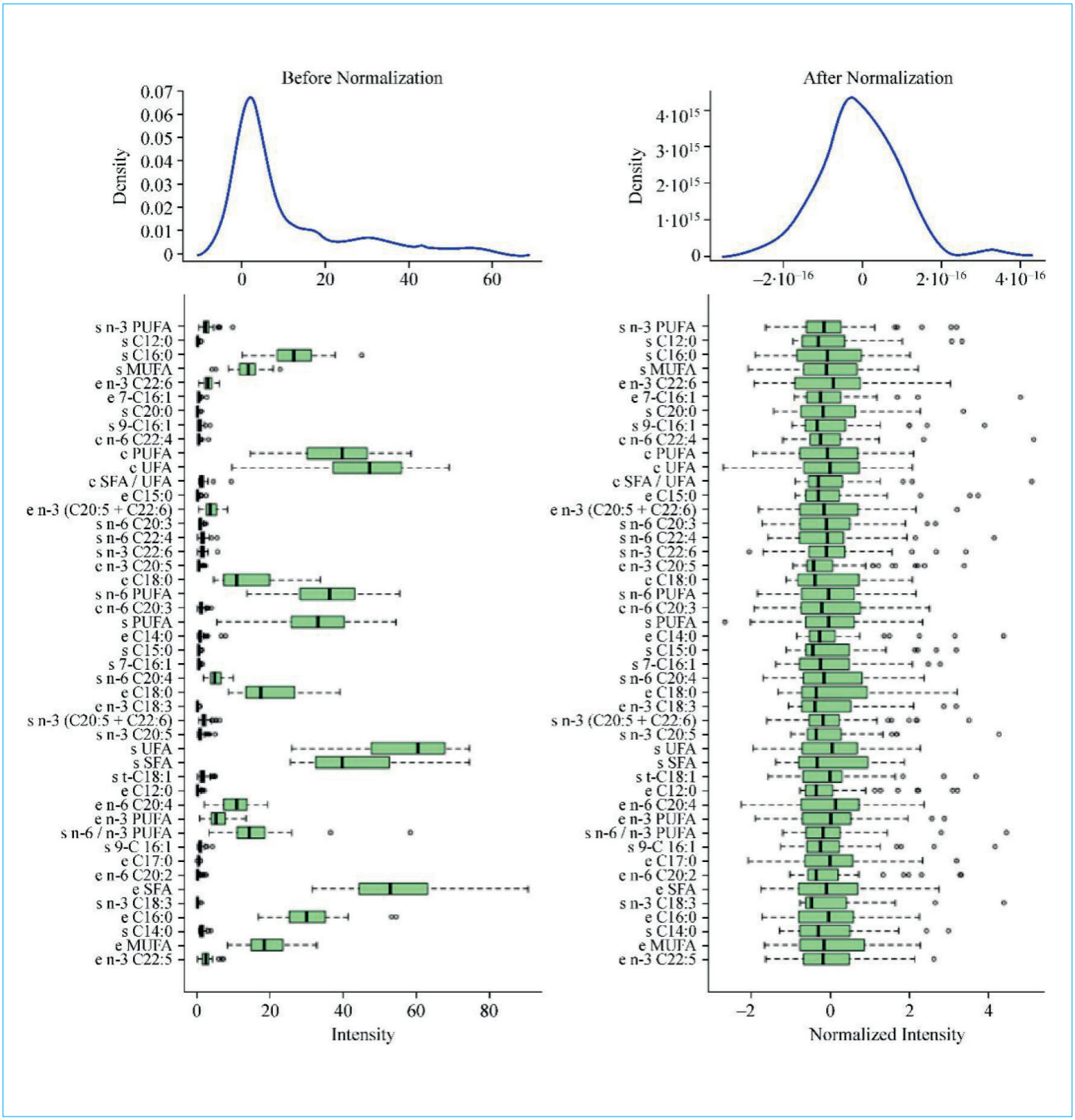

Figure 1. Normalization of fatty acid levels in erythrocyte membranes and blood serum in patients with IBD, examined dynamically (left — parameters before normalization, right — after normalization)

Рисунок 1. Нормализация уровней жирных кислот мембран эритроцитов и сыворотки крови у пациентов с ВЗК, обследованных в динамике (слева — параметры до нормализации, справа — после нормализации)

C20:5n-3 + C22:6n-3; $p = 0.0018$) and omega-6 PUFA ($p = 0.033$). The ratio of SFA/PUFA was lower in erythrocyte membranes in the remission stage ($p = 0.039$) and higher in serum than in controls ($p = 0.04$). In the inactive stage, patients with IBD had higher levels of individual omega-6 PUFAs both of C16:2n-6 ($p = 0.000003$), C20:2n-6 ($p = 0.000006$), C20:3n-6 ($p = 0.0005$) in erythrocyte membranes and C20:4n-6 ($p = 0.036$), C22:4n-6 ($p = 0.001$) in serum than in the comparison group. Individual omega-3 PUFAs were also predominant in erythrocyte membranes of patients with inactive IBD compared to healthy individuals: C18:3n-3 ($p = 0.00006$), C20:5n-3 ($p = 0.000001$), C22:5n-3 ($p = 0.0006$), C22:6n-3 ($p = 0.033$). But the total content of omega-3 PUFAs was higher compared to omega-6 PUFAs in erythrocyte membranes of patients with IBD in remission, therefore the ratio of omega-3/omega-6 PUFAs was higher than in comparison group subjects ($p = 0.05$).

Analysis of changes in fatty acid levels in patients with IBD in the dynamics of observation (exacerbation vs. remission) showed greater informativeness of erythrocyte membranes compared to serum. The predominance of the sum of saturated fatty acids over unsaturated ones in the erythrocyte membranes of patients with IBD in the stage of exacerbation ($p = 0.0019$), affected the higher values of SFA/UFA ($p = 0.01$) and SFA/PUFA ($p = 0.02$) ratios, than in the remission stage. A greater proportion of SFAs in erythrocyte membranes was found to be associated with a higher content of palmitic C16:0 ($p = 0.015$) and stearic C18:0 ($p = 0.0005$) acids, the mass fraction of which was higher compared to other SFAs. Serum levels of C20:0 ($p = 0.01$) were found to be higher in exacerbations. Levels of a whole list of SFAs, the percentage of which in erythrocyte membranes is low, were higher in remission: C12:0 ($p = 0.047$), C14:0 ($p = 0.057$), C15:0 ($p = 0.041$), C17:0 ($p = 0.021$).

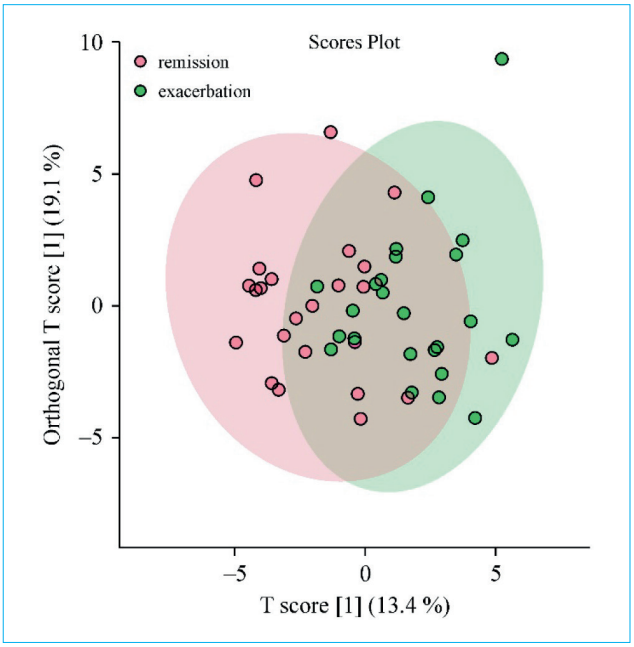

Figure 2. PLS DA method in the analysis of fatty acids in erythrocyte membrane and blood serum in patients with IBD, examined in dynamics: green cloud, green dots — in the acute stage; pink cloud, pink dots — in remission

Рисунок 2. Метод PLS DA при анализе уровней жирных кислот мембран эритроцитов и сыворотки крови у пациентов с ВЗК, обследованных в динамике: зеленое облако, зеленые точки — в стадии обострения; розовое облако, розовые точки — в стадии ремиссии

The total content of UFAs was higher in the remission stage than in the exacerbation of IBD, including polyunsaturated, both omega-3 and omega-6 FAs: UFAs — $p = 0.001$; PUFAs — $p = 0.0009$; omega-3 PUFAs — $p = 0.004$; omega-6 PUFAs — $p = 0.0009$.

It should be noted that the levels of individual omega-6 PUFAs were statistically significantly higher in remission compared to exacerbation: C16:2n-6 ($p = 0.002$), C18:2n-6 ($p = 0.0001$), C20:2n-6 ($p = 0.002$), C20:3n-6 ($p = 0.004$), C20:4n-6 ($p = 0.064$), C22:4n-6 ($p = 0.001$).

At the second stage, to determine the FAs levels in erythrocyte membrane and in serum as potential predictors of exacerbation, the concentrations of the indicators were normalized by their sum (Fig. 1).

Discriminant analysis (PLS DA) made it possible to establish the presence of different levels of fatty acids in erythrocyte membranes and blood serum in the acute and remission stages (Fig. 2).

The Volcano plot method, which is a combination of multiple changes and t-tests, was applied in the subsequent analysis (Fig. 3). Ten fatty acids (red and pink dots) levels of which differed statistically significantly between active and inactive stages of the disease can be seen from the plot data.

The Table presents data on erythrocyte and serum membrane fatty acids, potential predictors of exacerbation in patients with IBD.

It follows from the data of the Table that the stage of exacerbation in patients with IBD, examined in dynamics, is associated with higher levels of stearic acid C18:0 ($p = 0.005$), SFA/UFA ($p = 0.034$) and SFA/PUFA ($p = 0.039$) ratios in erythrocyte membranes, serum level of arachidic acid C20:0 ($p = 0.008$), and conversely, lower levels of UFAs in erythrocyte membranes: eicosapentaenoic C20:5n-3 ($p = 0.0023$),

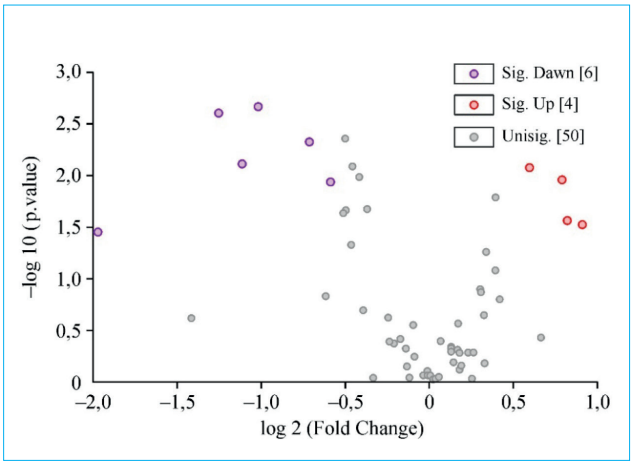

Figure 3. Volcano plot (paired statistics) of fatty acids of erythrocyte membranes and blood serum in the identification of markers-predictors of exacerbation

Рисунок 3. Volcano plot (парная статистика) жирных кислот мембран эритроцитов и сыворотки крови в выявлении маркеров — предикторов обострения

eicosa-diene C20:2n-6 ($p = 0.0027$), hexadecadiene C16:2n-6 ($p = 0.006$), docosatetraenoic C22:4n-6 ($p = 0.008$) and alpha-linolenic C18:3n-3 ($p = 0.039$).

Figure 4 shows the distribution of erythrocyte membrane and blood serum fatty acids according to their contribution to distinguishing between exacerbation and remission in patients with IBD examined dynamically.

ROC analysis revealed sufficient levels of diagnostic accuracy when using levels of individual fatty acids with high values of either sensitivity or specificity to differentiate between stages of exacerbation and remission of IBD (Fig. 5). For example, erythrocyte eicosadienoic acid C20:2n-6 content provided an AUC of 0.774 (95 % CI: 0.621–0.878) with a sensitivity of 66.7 % and specificity 79.2 %; erythrocyte stearic acid C18:0 — AUC 0.767 (95 % CI: 0.61–0.878), sensitivity — 70.8 %, specificity — 70.8 %; erythrocyte alpha-linolenic

Table. Indicators of fatty acids of erythrocyte membranes and blood serum and their ratios — potential predictors of exacerbation in patients with IBD (exacerbation vs. remission); data obtained using Volcano plot (paired statistics)

Таблица. Показатели жирных кислот мембран эритроцитов и сыворотки крови и их соотношения — потенциальные предикторы обострения у пациентов с ВЗК (обострение против ремиссии); данные получены при использовании Volcano plot (парная статистика)

Fatty acids / *Жирные кислоты*	**Frequency of changes (FC) *Кратность изменений***	**log2(FC)**	***p* value (raw.p val.) *Значения p***	**−log10(*p*)**
Erythrocyte eicosapentaenoic acid *Эритроцитарная эйкозапентаеновая кислота* C20:5n-3	0.50912	−0.97391	0.002327	2.6332
Erythrocyte eicosadienoic acid *Эритроцитарная эйкозадиеновая кислота* C20:2n-6	0.43428	−1.2033	0.002768	2.5578
Erythrocyte stearic acid *Эритроцитарная стеариновая кислота* C18:0	1.5551	0.63699	0.005021	2.2992
Erythrocyte octadecadienic acid *Эритроцитарная гексадекадиеновая кислота* C16:2n-6	0.48007	−1.0587	0.006332	2.1985
Serum arachidic acid *Сывороточная арахиновая кислота* C20:0	1.7652	0.81986	0.00819	2.0867
Erythrocyte docosatetraenoic acid *Эритроцитарная докозатетраеновая кислота* C22:4n-6	0.63131	−0.66357	0.008351	2.0783
Erythrocyte SFA/UFA ratio Эритроцитарное соотношение НЖК/ННЖК	1.8178	0.86223	0.034264	1.4652
Erythrocyte alpha-linolenic acid *Эритроцитарная альфа-линоленовая кислота* C18:3n-3	0.26412	−1.9207	0.039344	1.4051
Erythrocyte SFA/PUFA ratio *Эритроцитарное соотношение НЖК/ПНЖК*	1.9341	0.95165	0.03984	1.3997

Note: *SFA — saturated fatty acids, UFA — unsaturated fatty acids, PUFA — polyunsaturated fatty acids.*
Примечание: *НЖК — насыщенные жирные кислоты, ННЖК — ненасыщенные жирные кислоты, ПНЖК — полиненасыщенные жирные кислоты.*

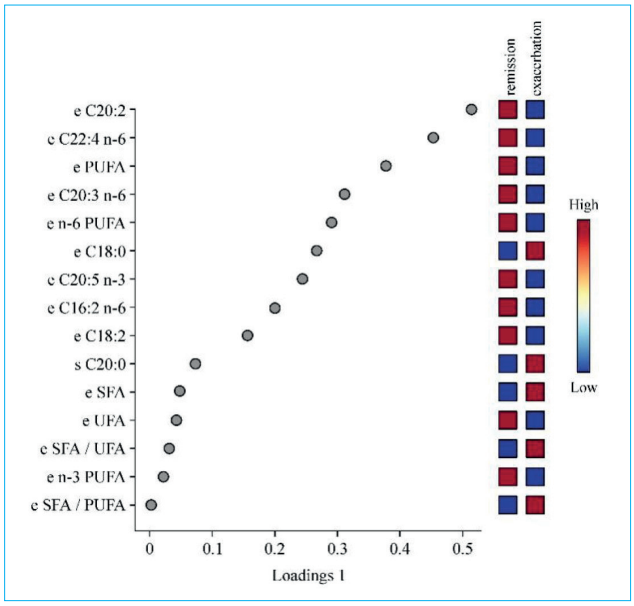

Figure 4. Distribution of fatty acids of erythrocyte membranes and blood serum according to their degree of contribution to distinguishing the stage of exacerbation and remission in patients with IBD examined dynamically

Рисунок 4. Распределение жирных кислот мембран эритроцитов и сыворотки крови по их степени вклада в различение стадии обострения и ремиссии у пациентов с ВЗК, обследованных в динамике

acid C18:3n-3 — AUC 0.766 (95 % CI: 0.606–0.899), sensitivity — 66.7 %, specificity — 75.1 %; serum arachidic acid C20:0 — AUC 0.727 (95 % CI: 0.569–0.859), sensitivity — 66.7 %, specificity — 75.1 %. A combined fatty acid model consisting of C20:2n-6 and C18:0 concentrations in erythrocyte membranes and C20:0 content in serum provided a lower AUC of 0.683 (95 % CI: 0.500–0.844), but a higher sensitivity — 91.4 %.

At the subsequent stage of statistical processing, the levels of the above mention fatty acids (C20:5n-3, C20:2n-6, C18:0, C16:2n-6, C22:4n-6, C18:3n-3), the ratios of SFA/UFA and SFA/PUFA in erythrocyte membranes, and the content of C20:0 in serum were used as biomarkers in cluster analysis of 48 patients with IBD in remission. The majority of patients with different nosological forms of IBD were found to be within one of these three clusters (Fig. 6).

The follow-up of the patients during the next year revealed some regularities. Patients with IBD, who were within the cluster with minimally changed FAs levels, had remission during 12 months of follow-up. The majority of individuals with IBD who were within the cluster with moderately altered FAs levels had an exacerbation from 6 to 8 months from the beginning of monitoring. The shortest terms before the onset of the active stage of the disease were in patients with maximally deviated FAs values — 2–4 months. Patients who were placed in the clusters intersection areas appeared in the stage of exacerbation in intermediate terms in comparison with those described above. Thus, fatty acid levels have the potential to predict exacerbation of IBD and stratify the risk of disease activity.

Discussion

The problem of searching for biomarkers — predictors of exacerbation development in patients with IBD continues to be relevant. From the point of view of accessibility and minimally invasiveness, the study of fatty acids of erythrocyte membranes and blood serum has certain advantages. Fatty acids, as essential components of dietary lipids, play a variety of roles in IBD, ranging from pro-/anti-inflammatory and immunoregulatory functions to modulation of the gut microbiota and maintenance of the intestinal barrier. Short-chain fatty acids, products of the fermentation of non-digestible dietary fibre by the gut microbiota, have strong anti-inflammatory properties and are considered as key protective factors in IBD. Among long-chain fatty acids, saturated fatty acids, trans-isomers of fatty acids and omega-6 PUFAs have pro-inflammatory effects, while oleic acid and omega-3 PUFAs have anti-inflammatory effects. PUFA-derived lipid mediators are bioactive molecules that influence immune cell function and exert both pro- and anti-inflammatory effects. Recent studies have highlighted the potential of medium and very long chain fatty acids in modulating inflammation, mucosal barriers and intestinal microbiota in IBD [6]. Thus, the consideration of fatty acid levels in erythrocyte membranes and blood serum as potential biomarkers of exacerbation prediction in IBD is pathogenetically justified.

In the present study, erythrocyte membrane fatty acids were the most informative, which is not surprising since they reflect the metabolic profile to a greater extent than serum fatty acids, which are more dependent on dietary characteristics [11]. The general trend revealed was an increased content of saturated fatty acids, both total one and the content of individual fatty acids levels — stearic acid, arachidic acid — and a decreased content of unsaturated fatty acids, including polyunsaturated fatty acids.

The proinflammatory effects of saturated fatty acids are realized through the effect on the peroxisome proliferator-activated receptor gamma (PPAR-γ) and retinoid X receptors (RXR) [12]. It has been previously shown that total saturated fatty acid content, as well as levels of individual

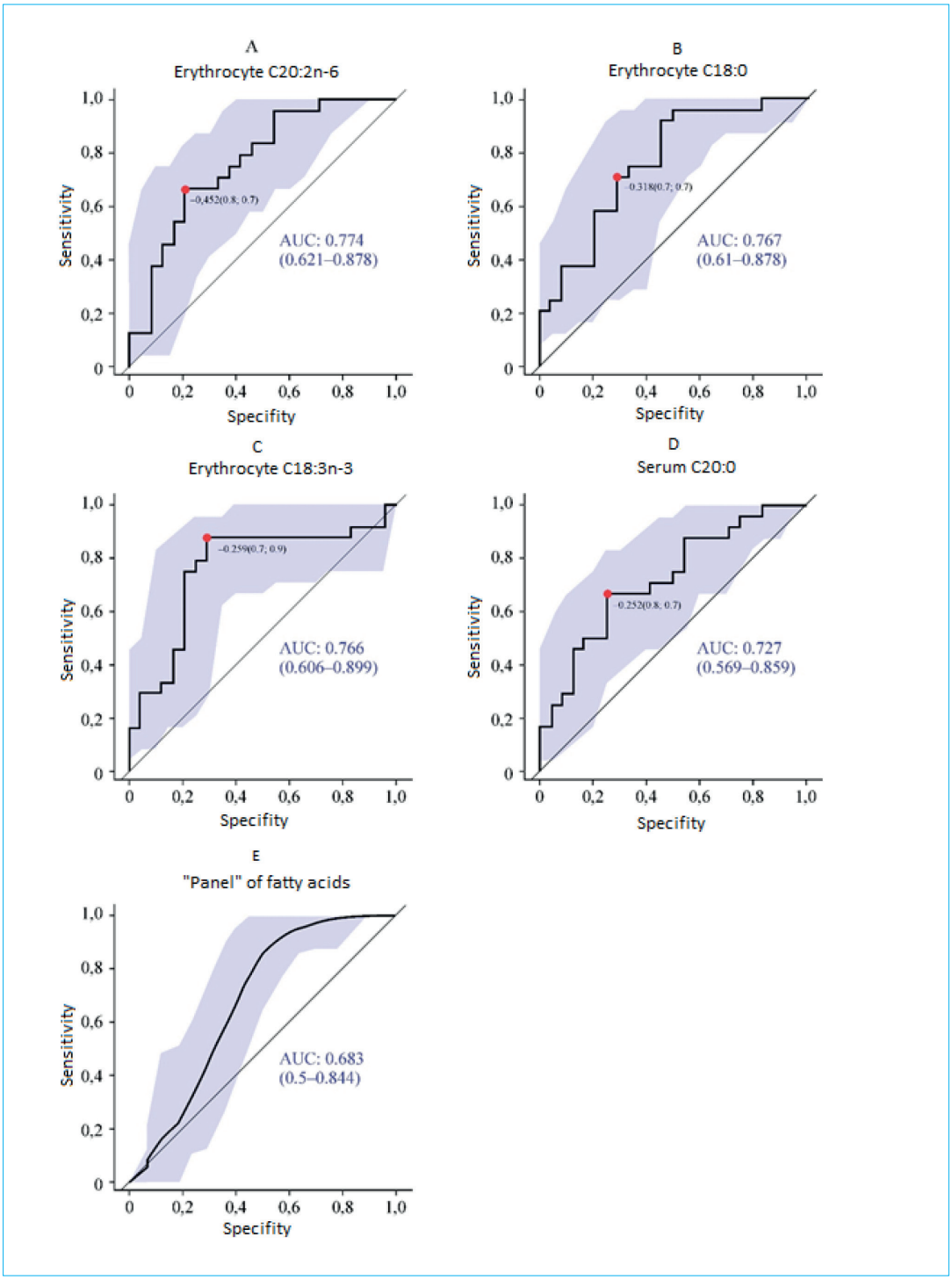

Figure 5. ROC curves including fatty acid levels to distinguish between exacerbation and remission of IBD in patients examined dynamically: A — erythrocyte eicosadienoic acid C20:2n-6 (AUC 0.774; 95 % CI: 0.621–0.878); B — erythrocyte stearic acid C18:0 (AUC 0.767; 95 % CI: 0.61–0.878); C — erythrocyte alpha-linolenic acid C18:3n-3 (AUC 0.766; 95% CI: 0.606–0.899); D — serum arachidic C20:0 (AUC 0.727; 95 % CI: 0.569–0.859); E — "panel" of fatty acids (erC20:2n-6, erC18:0, serumC20:0) (AUC 0.683; 95 % CI: 0.500–0.844)

Рисунок 5. ROC-кривые с включением уровней жирных кислот для различения обострения и ремиссии ВЗК у пациентов, обследованных в динамике: А — эритроцитарная эйкозадиеновая кислота С20:2n-6 (AUC 0,774; 95% ДИ: 0,621–0,878); В — эритроцитарная стеариновая кислота С18:0 (AUC 0,767; 95% ДИ: 0,61–0,878); С — эритроцитарная альфа-линоленовая кислота С18:3n-3 (AUC 0,766; 95% ДИ: 0,606–0,899); D — сывороточная арахиновая С20:0 (AUC 0,727; 95% ДИ: 0,569–0,859); Е — «панель» жирных кислот (эрС20:2n-6, эрС18:0, сывС20:0) (AUC 0,683; 95% ДИ: 0,500–0,844)

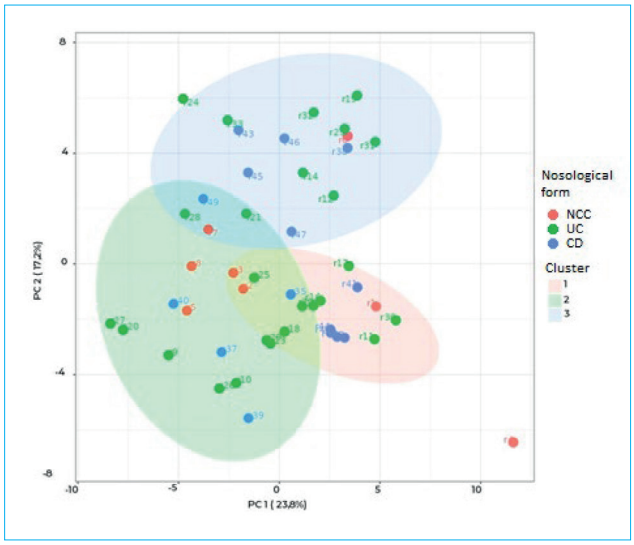

Figure 6. Cluster analysis using fatty acid levels of erythrocytes membranes and blood serum — potential predictors of IBD exacerbation in a group of patients in remission (n = 48). Blue cloud — cluster of patients with minimally altered FAs levels; green — cluster of patients with moderately altered FAs levels; pink — cluster of patients with maximally altered FAs levels. Red dots — patients with unclassifiable colitis, green — patients with ulcerative colitis, blue — patients with Crohn's disease

Рисунок 6. Кластерный анализ с использованием уровней ЖК мембран эритроцитов и сыворотки крови — потенциальных предикторов обострения ВЗК у группы пациентов в стадии ремиссии (n = 48). Голубое облако — кластер пациентов с минимально измененными уровнями ЖК; зеленое — кластер пациентов с умеренно измененными уровнями ЖК; розовое — кластер пациентов с максимально измененными уровнями ЖК. Красные точки — пациенты с неклассифицируемым колитом, зеленые — пациенты с язвенным колитом, синие — пациенты с болезнью Крона

saturated fatty acids — palmitic acid, stearic acid and arachidic acid — were directly associated with levels of inflammatory markers, including leukocyte counts, blood sedimentation rate, C-reactive protein, fibrinogen, and fecal calprotectin [13]. Saturated fatty acids have been shown to be associated with macrophage inflammation and lipotoxicity [14], that is due to their less efficient esterification into triglycerides. Accumulation of palmitic acid in macrophages stimulates them to increased release of inflammatory cytokines in the intestinal mucosa, supporting inflammation [15]. Studies on plasma metabolites have shown that palmitic acid is a potential diagnostic marker for IBD [16]. It promotes inflammation by increasing intestinal epithelial permeability [17], activating the NF-κB pathway and cytokines [18], causing endoplasmic reticulum stress leading to lipotoxicity of intestinal epithelial cells [19]. The proinflammatory potential of saturated FAs is indirectly confirmed by direct associations of their levels in serum with concentrations of tissue cytokines in patients with ulcerative colitis [20].

A number of experimental studies have shown significant changes in fatty acid metabolism under conditions of hypoxia associated with inflammation and carcinogenesis through HIF1α-dependent and independent mechanisms [21, 22]. Activation of fatty acid synthase, an enzyme of de novo lipogenesis, in IBD can modulate the permeability of the intestinal barrier through covalent attachment of palmitic acid to mucin-2, a key intestinal glycoprotein [23, 24].

Reduced levels of unsaturated fatty acids, including polyunsaturated fatty acids, was another important trend identified in the present study. Reduced levels of both omega-3 (eicosapentaenoic acid, alpha-linolenic acid) and omega-6 PUFAs (eicosadienoic acid, hexadecadienoic acid, docosatetraenoic acid) were found to be predictors of exacerbation development.

PUFAs may influence the course of IBD by affecting inflammation in the intestinal wall. Increased arachidonic acid [25, 26] and decreased eicosapentaenoic acid [27, 28] have been found to be associated with inflammation in the colonic mucosa of patients with ulcerative colitis. PUFAs can modulate anti-inflammatory signaling pathways and maintain the integrity of the intestinal barrier by interacting with G-protein coupled receptor 120 (GPR120) [29, 30]. The anti-inflammatory effects of omega-3 PUFAs have been associated with a decrease in prostaglandin E_2 (PGE_2) levels, alkaline phosphatase activity [25], NF-κB, TNF-alpha, inducible nitric oxide synthase and interleukin 1 beta levels [31], and an increase in PPAR-γ activity [32]. Alpha-linolenic acid can reduce the activity of ionized calcium-binding adaptor molecule 1-positive macrophages [33] and decrease the expression of pro-inflammatory genes IL-8, cyclooxygenase-2 (COX2) and inducible nitric oxide synthase with decreased inflammation in the gut [34].

Eicosapentaenoic acid slowed down the inflammatory pathways of transforming growth factor beta-1/epidermal growth factor receptor P-EGFR and NF-κB, modulated the reductive-oxidative balance and mitigated the progression of UC in a rat experiment [35]. In studies, docosahexaenoic acid and eicosapentaenoic acid were shown to reduce the severity of endoplasmic reticulum stress in bocaloid cells, affecting the synthesis and secretion of protective mucin barrier mucin-2 (Muc2) [19].

E. Scaioli et al. evaluated the ability of free eicosapentaenoic acid (EPA-FFA) form to reduce intestinal inflammation in patients with UC and used fecal calprotectin level as a marker [27]. The study showed that compounds derived from omega-3 PUFAs can not only induce but also maintain clinical remission for at least six months. A. Prossomariti et al. showed that supplementation with EPA-FFAs reduces inflammation of the intestinal mucosa, promotes the differentiation of bocaloid cells and changes the composition of the intestinal microbiota in patients with UC [36].

K. Uchiyama et al. also investigated the effect of dietary therapy using 'omega-3 PUFA exchange table' (ω3DP) on the composition of erythrocyte membranes of patients with CD and UC and their remission. It can be assumed that ω3DP changes the composition of cell membranes of FA and affects the clinical activity of patients with IBD [37].

The significance of reduced levels of a number of omega-3 PUFAs in the present study as predictors of exacerbation development may be related to the above effects of these metabolites.

J. Diab et al. established the potential of increased levels of arachidonic acid derivatives (prostaglandins E_2 and D_2, thromboxane B_2, hydroperoxyecosatetraenoic acids) in colon tissue in predicting the development of active inflammation in ulcerative colitis [38].

According to the present work, the reduced level of omega-6 PUFA — eicosadienoic acid (C20:2n-6) turned out to be a predictor of exacerbation development in patients with IBD. The concentrations of this acid in tissues and body fluids are significantly lower than linoleic and arachidonic acids [39, 40]. The concentration of C20:2n-6 in blood indirectly reflects the level of other omega-6 PUFAs and, probably, may depend both on the level of its precursor, linoleic acid (C18:2n-6), and on the degree of activity of endogenous synthesis of arachidonic acid, which is a derivative of C20:2n-6 [41].

Analyses of the effect of eicosadienoic FA on inflammatory processes revealed opposite effects. The anti-inflammatory nature of the effect of C20:2n-6 in patients with type 2 diabetes mellitus in a large-scale European study [42, 43], in autoimmune diseases (polymyositis, dermatomyositis) was shown [44]. Increased activity of Δ6-desaturase (D6D, FADS2 gene), which determines high levels of C20:2n-6, C20:4n-6, and a number of other PUFAs in blood plasma, may be associated with the rs174537 polymorphism in the FADS gene cluster affecting the concentrations of low-density lipoproteins and total cholesterol [45–47]. The results of experimental and clinical studies suggest that eicosadienoic acid is an anti- rather than pro-inflammatory metabolite [48, 49]. The study by S. Sitkin et al. proposed a new metabolomic index — the ratio of the level of arachidonic acid to the level of eicosadienoic acid (C20:4n-6/C20:2n-6), reflecting the balance between pro-inflammatory and anti-inflammatory components of the omega-6 PUFA pool [50].

Since the synthesis of docosatetraenoic acid C22:4n-6 occurs through the action of elongases on arachidonic acid C20:4n-6, the consumption of the latter in the arachidonic cascade during the development of inflammation leads to a decrease in docosatetraenoic acid due to the low level of substrate for its formation [6].

To confirm our results, a larger cohort including patients with IBD of different severity, longer follow-up periods are required; this may improve the quality of the prognostic model.

Conclusion

Thus, the study revealed the peculiarities of fatty acid profile of erythrocyte membranes and blood serum of patients with IBD examined in dynamics. Higher levels of stearic FA C18:0 ($p = 0.005$), SFA/UFA ($p = 0.034$) and SFA/PUFA ($p = 0.039$) ratios in erythrocyte membranes, arachidic acid C20:0 ($p = 0.008$) in blood serum, and in contrast, lower concentrations of unsaturated fatty acids were revealed in erythrocyte membranes: eicosapentaenoic C20:5n-3 ($p = 0.0023$), eicosadiene C20:2n-6 ($p = 0.0027$), hexadecadiene C16:2n-6 ($p = 0.006$), docosatetraenoic C22:4n-6 ($p = 0.008$) and alpha-linolenic C18:3n-3 ($p = 0.039$).

The use of levels of individual fatty acids in blood serum and erythrocyte membranes provided sufficient levels of diagnostic accuracy in distinguishing between exacerbation and remission in patients with IBD examined in dynamics. A combined panel of fatty acids including C20:2n-6, C18:0 levels in erythrocyte membranes and C20:0 content in serum showed an AUC of 0.683 (95 % CI: 0.500–0.844) with a higher sensitivity (91.4 %) and a low specificity (68.3 %).

Levels of C20:5n-3, C20:2n-6, C18:0, C16:2n-6, C22:4n-6, C18:3n-3 fatty acids, ratios of SFA/UFAs and SFAs/PUFAs in erythrocyte membranes and the content of C20:0 in blood serum, used as biomarkers-predictors of exacerbation development in patients with IBD in remission, predicted the development of IBD exacerbation in 2–4 months in case of maximally altered FA levels, in 6–8 months — in case of moderately altered FA levels, and remission persistence for 12 months — in case of minimally altered FA levels.

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