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Gut Microbiota, Tryptophan Metabolism, Quality of Life, Psychoemotional and Cognitive Impairments in Functional Constipation

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Aim: to investigate the relationship between tryptophan metabolism features, gut microbiota composition, systemic inflammation markers, cortisol levels, quality of life, and psychoemotional and cognitive status in female patients with functional constipation (FC).

Materials and methods. The study included 64 female patients with FC and 26 age- and BMI-matched women without FC ($p > 0.05$). All participants underwent assessment of gut microbiota composition in stool samples (via 16S rRNA sequencing), health-related quality of life (SF-36), psychoemotional status (4DSQ, Spielberger — Hanin test, Hamilton scale), and cognitive function (BACS cognitive tests). Tryptophan metabolism was evaluated by measuring levels of interleukin-1β, cortisol, brain-derived neurotrophic factor (BDNF), tryptophan, kynurenine, kynurenic acid, and serum and platelet serotonin.

Results. Compared to women without FC, female patients with FC had higher levels of cortisol (325 [266; 403] vs. 275 [255; 304] nmol/L; $p = 0.025$), interleukin-1β (10.0 [9.2; 11.2] vs. 7.2 [6.5; 7.8] pg/mL; $p < 0.001$), and blood kynurenine (0.65 [0.54; 0.82] vs. 0.44 [0.35; 0.48] μg/mL; $p < 0.001$), as well as lower plasma serotonin levels (108 [85; 134] vs. 163 [117; 190] ng/mL; $p < 0.001$). No differences were found between groups in plasma tryptophan, BDNF, kynurenic acid, or platelet serotonin. Patients with FC exhibited more pronounced depression (Hamilton scale: 8 [6; 9] vs. 3 [2; 3] points; $p < 0.001$) and somatization (9 [7; 12] vs. 5 [3; 9] points; $p < 0.001$); lower cognitive function scores (50 [45; 54] vs. 54 [53; 56] points; $p < 0.001$), particularly in auditory-verbal memory ($p < 0.001$) and information processing speed ($p < 0.001$); and reduced quality of life (SF-36) in physical functioning (90 [83; 95] vs. 95 [95; 95] points; $p < 0.001$) and bodily pain (60 [50; 70] vs. 75 [56; 85] points; $p < 0.001$). Cortisol levels positively correlated with bodily pain ($r = 0.379$; $p = 0.003$), while interleukin-1β levels inversely correlated with bodily pain ($r = -0.391$; $p = 0.002$), physical functioning ($r = -0.448$; $p < 0.001$), and verbal memory ($r = -0.252$; $p = 0.046$), and positively correlated with depression ($r = 0.311$; $p = 0.013$) and somatization ($r = 0.266$; $p = 0.035$). Cortisol levels correlated positively with *Oscillospira* ($r = 0.45$; $p = 0.01$), while kynurenine levels correlated with *Alistipes* ($r = 0.36$; $p = 0.04$) abundance. Plasma serotonin positively correlated with *Haemophilus* ($r = 0.37$; $p = 0.03$) and inversely with *Bacteroides plebeius* ($r = -0.40$; $p = 0.02$) abundance. Physical functioning (SF-36) positively correlated with *Lachnospiraceae* NK4B4 group ($r = 0.35$; $p = 0.04$), while depression severity (4DSQ) inversely correlated with *Alistipes* abundance ($r = -0.37$; $p = 0.03$). Information processing speed is inversely correlated with abundance of *Bacilli* ($r = -0.48$; $p = 0.004$), *Lactobacillales* ($r = -0.48$; $p = 0.004$), *Pasteurellales* ($r = -0.36$; $p = 0.03$), *Pasteurellaceae* ($r = -0.36$; $p = 0.03$), *Streptococcaceae* ($r = -0.47$; $p = 0.006$), *Haemophilus* ($r = -0.41$; $p = 0.02$), and *Streptococcus* ($r = -0.38$; $p = 0.02$).

Conclusion. The findings indicate that women with functional constipation exhibit altered tryptophan metabolism and gut microbiota dysbiosis, associated with depression, somatization, cognitive impairment, and reduced health-related quality of life.

Keywords: gut microbiota, microbiome, functional constipation, depression, anxiety, quality of life, SF-36, cognitive function, somatization, tryptophan, serotonin, kynurenine, interleukin, cortisol

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Кишечная микробиота, метаболизм триптофана, качество жизни, психоэмоциональные и когнитивные нарушения при функциональном запоре

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Цель: изучить взаимосвязь между особенностями метаболизма триптофана, составом кишечной микробиоты, маркерами системного воспаления и кортизолом, качеством жизни, а также состоянием психоэмоциональной и когнитивной сфер у пациенток с функциональным запором (ФЗ).

Материалы и методы. В исследование было включено 64 пациентки с ФЗ и 26 женщин без ФЗ, сопоставимых по возрасту и ИМТ ($p > 0,05$). Всем испытуемым проводилась оценка состава кишечной микробиоты в образцах кала (с помощью секвенирования 16S рРНК), связанного со здоровьем качества жизни (SF-36), состояния психоэмоциональной сферы (4DSQ, тест Спилбергера — Ханина, шкала Гамильтона), когнитивного статуса (когнитивные тесты BACS). Для оценки метаболизма триптофана исследовались уровни интерлейкина-1β, кортизола, нейротрофического фактора головного мозга, триптофана, кинуренина, кинурениновой кислоты, сывороточного и тромбоцитарного серотонина.

Результаты. В отличие от женщин без ФЗ, пациентки с данным заболеванием имели более высокие уровни кортизола (325 [266; 403] vs. 275 [255; 304] нмоль/л; $p = 0,025$), интерлейкина-1β (10,0 [9,2; 11,2] vs. 7,2 [6,5; 7,8] пг/мл; $p < 0,001$) и кинуренина в крови (0,65 [0,54; 0,82] vs. 0,44 [0,35; 0,48] мкг/мл; $p < 0,001$), а также меньший уровень серотонина плазмы (108 [85; 134] vs. 163 [117; 190] нг/мл; $p < 0,001$). При этом содержание триптофана, нейротрофического фактора головного мозга и кинурениновой кислоты в плазме крови и серотонина в тромбоцитах не различалось между группами. У пациенток с ФЗ наблюдались более выраженная депрессия по шкале Гамильтона (8 [6; 9] vs. 3 [2; 3] баллов; $p < 0,001$) и соматизация (9 [7; 12] vs. 5 [3; 9] баллов; $p < 0,001$); меньшие показатели когнитивной функции (50 [45; 54] vs. 54 [53; 56] баллов; $p < 0,001$), в том числе ответственной за слухоречевую память ($p < 0,001$) и скорость обработки информации ($p < 0,001$); снижение параметров качества жизни по опроснику SF-36 по шкалам физического функционирования (90 [83; 95] vs. 95 [95; 95] баллов; $p < 0,001$) и телесной боли (60 [50; 70] vs. 75 [56; 85] баллов; $p < 0,001$). Уровень кортизола прямо коррелировал с показателем качества жизни по шкале телесной боли ($r = 0,379$; $p = 0,003$), а уровень интерлейкина-1β — обратно со шкалами телесной боли ($r = –0,391$; $p = 0,002$), физического функционирования ($r = –0,448$; $p < 0,001$) и вербальной памяти ($r = –0,252$; $p = 0,046$), а также прямо с выраженностью депрессии ($r = 0,311$; $p = 0,013$) и соматизации ($r = 0,266$; $p = 0,035$). Уровень кортизола прямо коррелировал с обилием бактерий рода *Oscillospira* ($r = 0,45$; $p = 0,01$), а кинуренина — с *Alistipes* ($r = 0,36$; $p = 0,04$); содержание серотонина в плазме прямо коррелировало с обилием представителей рода *Haemophilus* ($r = 0,37$; $p = 0,03$) и обратно — с *Bacteroides plebeius* ($r = –0,40$; $p = 0,02$). Обнаружена прямая корреляция показателей качества жизни по шкале физического функционирования с обилием представителей рода *Lachnospiraceae* NK4B4 ($r = 0,35$; $p = 0,04$) и обратная корреляция выраженности депрессии (4DSQ) с уровнем *Alistipes* ($r = –0,37$; $p = 0,03$). Также выявлена обратная корреляция скорости обработки информации с обилием представителей класса *Bacilli* ($r = –0,48$; $p = 0,004$), порядков *Lactobacillales* ($r = –0,48$; $p = 0,004$) и *Pasteurellales* ($r = –0,36$; $p = 0,03$), семейств *Pasteurellaceae* ($r = –0,36$; $p = 0,03$) и *Streptococcaceae* ($r = –0,47$; $p = 0,006$), родов *Haemophilus* ($r = –0,41$; $p = 0,02$) и *Streptococcus* ($r = –0,38$; $p = 0,02$).

Заключение. Согласно полученным результатам, у пациенток с функциональным запором изменен метаболизм триптофана и нарушен состав кишечной микробиоты, что сопровождается развитием депрессии и соматизации, нарушением когнитивной функции и снижением качества жизни, связанного со здоровьем.

Ключевые слова: кишечная микробиота, микробиом, функциональный запор, депрессия, тревога, качество жизни, SF-36, когнитивная функция, соматизация, триптофан, серотонин, кинуренин, интерлейкин, кортизол

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Introduction

Functional constipation (FC) is a functional gastrointestinal disorder characterized by symptoms of difficult, infrequent, or incomplete defecation [1]. FC affects 1.9–40.1 % of the adult population, with a higher prevalence among women [1, 2].

FC negatively impacts patients' quality of life to a degree comparable to type 2 diabetes, gastroesophageal reflux disease, and irritable bowel syndrome [2]. Anxiety and depressive disorders are common among FC patients, worsening their condition and further impairing quality of life. Depression is reported as the most frequent emotional disorder in these patients [3].

A potential shared mechanism underlying both impaired colonic motility and these psychoemotional disturbances in FC may involve altered tryptophan metabolism due to gut microbiota dysbiosis. The human microbiota consists of microorganisms (bacteria, fungi, viruses, archaea, and some eukaryotes) inhabiting mucosal surfaces and the skin [4]. The most abundant and diverse microbiota resides in the gastrointestinal (GI) tract, influencing numerous physiological processes through metabolic, synthetic, and immunomodulatory functions [5].

Experiments in rodents have shown that changes in gut microbiota composition are closely linked to altered serotonin metabolism and impaired colonic motility [6, 7]. For example, germ-free mice colonized with microbiota from healthy donors exhibited higher levels of serotonin and its synthesizing enzyme tryptophan hydroxylase-1 (TPH-1) in intestinal tissues, along with significantly shorter colonic transit time, compared to mice colonized with microbiota from FC patients [6]. Additionally, fecal microbiota transplantation from healthy donors to FC patients has been shown to alleviate constipation symptoms and reduce anxiety and depressive disorders [7], highlighting the importance of microbial factors in the pathogenesis of these conditions.

The development of cognitive impairments due to colonic microbiota dysbiosis possibly shares similar pathogenic pathways [8]. However, the role of gut microbiota in the simultaneous disruption of psychoemotional status and cognitive function has not been previously explored.

Therefore, **the aim of this study** was to investigate the relationship between tryptophan metabolism, gut microbiota composition, systemic inflammation markers, quality of life, and psychoemotional and cognitive status in female patients with FC.

Materials and methods

Patients

The study was conducted at the Department of Chronic Intestinal and Pancreatic Diseases, V. Kh. Vasilenko Clinic of Propaedeutics of Internal Medicine, Gastroenterology, and Hepatology (Sechenovskiy University). It included 64 women aged from 18 to 65 years diagnosed with FC (study group) and 26 healthy women without constipation symptoms (control group). FC diagnosis was based on the Rome IV criteria [1] and clinical guidelines from the Russian Gastroenterological Association and the Russian Association of Coloproctology [9].

Exclusion criteria were:

– antibiotic or probiotic use within 4 weeks prior to the study;

– history of cancer, family history of colorectal cancer;

– previous GI surgeries;

– psychiatric disorders;

– renal insufficiency (creatinine clearance < 50 mL/min);

– hepatic insufficiency confirmed by clinical and laboratory tests.

All participants provided informed consent. The study was approved by the local Ethics Committee of Sechenovskiy University (Protocol No. 12-21, July 7, 2021).

Examinations

All enrolled female patients underwent the following tests:

– psychometric scale testing (assessment of anxiety and depression severity, cognitive abilities, and quality of life);

– clinical blood tests, urinalysis;

– blood tests (measurement of interleukin-1β, cortisol, brain-derived neurotrophic factor, tryptophan, kynurenine, kynurenic acid, serotonin, and platelet serotonin levels);

– 16S ribosomal RNA gene sequencing in stool samples.

All participants were assessed using the following psychometric tests:

– Hamilton Depression Rating Scale (HDRS) – interviewer-administered assessment of depression severity;

– Spielberger – Hanin State-Trait Anxiety Inventory (STAI) – self-reported anxiety evaluation;

– Four-Dimensional Symptom Questionnaire (4DSQ) – self-reported assessment of distress, depression, anxiety, and somatization;

– Brief Assessment of Cognition in Schizophrenia (BACS) – interviewer-administered cognitive function screening;

– SF-36 Questionnaire – self-reported quality of life assessment.

The cytokines and metabolites (except cortisol) were analyzed at the Exacte Labs laboratory (Director – Vasily I. Kazey, Cand. Sci. (Biol.)). Blood cortisol levels were measured at the Clinical Diagnostic Laboratory of Sechenovskiy University's Clinical Center (Head of the Central Laboratory and Diagnostic Service – Natalya M. Kashakanova). Venous blood samples were collected from participants in the morning (8:00–9:00 am) after fasting. Female patients and control group volunteers were advised to avoid tryptophan-rich foods (e.g., milk, chocolate, cheese) for 24 hours before sampling, as well as excessive physical activity and emotional stress on the day of blood collection.

Quantitative determination of the level of interleukin-1β and brain-derived neurotrophic factor (BDNF) was carried out by the sandwich ELISA method in blood serum using the ELISA kits HEA563Hu and SEA011Hu (Cloud-Clone Corp., USA). Analysis of the level of tryptophan, serotonin, kynurenic acid was carried out by the competitive ELISA method in blood serum using the CED720Ge, CEA808Ge, CED718Ge kits (Cloud-Clone Corp., USA), respectively. Determination of kynurenine was carried out similarly using the E01K0010 kit (BlueGene Biotech, China).

Platelet serotonin levels were analyzed by competitive ELISA in platelet-rich plasma supernatant using the E01H0106 kit (BlueGene Biotech, China). To collect the supernatant, the blood was subjected to sequential centrifugation at 1000 g at a temperature range from +2 °C to +8 °C for 15 minutes to obtain platelet-rich plasma, followed by sedimentation of the platelet mass. The resulting supernatants were frozen and stored at –80 °C until further use. Platelet mass was restored by adding 0.5 mL of 0.9% NaCl solution.

The blood cortisol level was assessed in the blood serum by electrochemiluminescence analysis using the 11-CRLHU-E01 Cortisol ELISA kit (Cloud-Clone Corp., USA) for the Cobas E601 apparatus (Switzerland).

16S rRNA Sequencing

The gut microbiome study was conducted at the V.A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences (Head of the Postgenomic Research Laboratory – Anna V. Kudryavtseva, Dr. Sci. (Biol.)). Fecal samples were self-collected by participants into sterile containers, immediately frozen, and stored at –80 °C. After thawing, samples were homogenized and centrifuged, with 400 µL of supernatant aliquoted for nucleic acid extraction. Total DNA was extracted using the MagNA Pure LC system (Roche, Switzerland). DNA quality and quantity were assessed with a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific, USA). 16S libraries were constructed following Illumina's 16S Metagenomic Sequencing Library Preparation protocol (MiSeq-compatible). The hypervariable V3–V4 regions of rRNA genes were amplified using primers CCTACGGGNGGCWGCAG (forward) and GACTACHVGGGTATCTAATCC (reverse), providing > 95 % bacterial coverage but minimal archaeal detection (Illumina-recommended). Amplicon size: ~450 bp. Library concentrations were measured with a Qubit 2.0 fluorometer (Invitrogen, USA) and the QuantiT dsDNA High-Sensitivity Assay Kit, followed by equimolar pooling. Pooled libraries were validated using an Agilent 2100 Bioanalyzer and the Agilent DNA 1000 Kit (Agilent Technologies, USA). Paired-end reads (2 × 300 nt) were generated on an Illumina MiSeq platform with the MiSeq Reagent Kit v2. Bioinformatics pipeline included: raw read filtering and error correction; Ribosomal Sequence Variant (RSV) identification using DADA2; merging of forward/reverse reads and chimera removal; taxonomic annotation against RDP and SILVA (v132) databases; downstream analysis with custom Python/R scripts (utilizing vegan, fossil, ggplot2 packages, etc.).

Statistical analysis

Data were analyzed using Statistica 10.0 (StatSoft Inc., USA). Quantitative data are presented as median and interquartile range.

Group comparisons were performed using the Mann — Whitney test. Spearman's correlation was used to assess relationships, with significance set at $p < 0.05$.

Results

The groups were comparable in age (38 [35–44] vs. 41 [33–45] years; $p = 0.678$). All participants showed no significant abnormalities in complete blood count, urinalysis, or basic biochemical markers (alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin, alkaline phosphatase, creatinine, urea, total protein, albumin, glucose, amylase, sodium, potassium) at the time of study enrollment.

FC patients had higher cortisol, interleukin-1β (IL-1β), and kynurenine levels and lower plasma serotonin levels compared to controls. The plasma serotonin-to-kynurenine ratio was also significantly lower in FC patients. No differences were observed in tryptophan, BDNF, kynurenic acid, or platelet serotonin levels (Table 1).

FC female patients showed poorer quality of life and emotional-cognitive health parameters compared to healthy controls (Table 2). Patients with FC had significantly lower quality of life scores in physical functioning and bodily pain (SF-36), worse overall cognitive status, verbal memory and information processing speed (BACS), along with higher somatization scores (4DSQ). While depression severity was significantly higher in FC patients during clinical interviews (HDRS), it appeared lower in self-reported assessments (4DSQ) compared to controls. Interestingly, FC patients demonstrated significantly better quality of life scores in the vitality domain (SF-36).

Significant differences in gut microbiota composition were observed at the class, order, family, genus, and species levels (Table 3). The most pronounced differences were at the genus and species levels (Fig. 1).

Despite significant differences in the abundance of bacterial taxa including the order *Caulobacterales*, family *Caulobacteraceae*, genera *Megamonas*, *Erysipelotrichaceae* UCG-006, *Alcaligenes*, *Brevundimonas*, *Alloscardovia, Daeguia*, and species *Negativibacillus massiliensis*, *Lactococcus raffinolactis*, *Alloscardovia omnicolens*, and *Coprobacter fastidiosus*, these microorganisms were detected in only a few patients (representing <0.3 % of all sequence reads) and were therefore excluded from subsequent correlation analysis.

Table 1. Markers of tryptophan metabolism in women with functional constipation and healthy women

Таблица 1. Биохимические маркеры путей метаболизма триптофана у пациенток с функциональным запором и клинически здоровых женщин

Biomarker ***Биомаркер***	**Patients with FC** ***Пациентки с ФЗ***	**Control group** ***Контрольная группа***	***p***
Cortisol, nmol/L *Кортизол, нмоль/л*	325.00 [266.00; 403.00]	275.00 [255.00; 304.00]	0.025
IL-1β, pg/mL *IL-1β, пг/мл*	10.0 [9.2; 11.2]	7.2 [6.5; 7.8]	<0.001
Tryptophan, μg/mL *Триптофан, мкг/мл*	3.8 [3.6; 4.0]	3.8 [3.4; 4.0]	0.820
BDNF, μg/mL *BDNF, мкг/мл*	1007 [880; 1264]	1057 [854; 1555]	0.637
Kynurenine, μg/mL *Кинуренин, мкг/мл*	0.65 [0.54; 0.82]	0.44 [0.35; 0.48]	<0.001
Kynurenic acid, ng/mL *Кинуреновая кислота, нг/мл*	26.0 [22.1; 30.5]	24.8 [23.7; 26.7]	0.447
Plasma serotonin, ng/mL *Серотонин плазмы, нг/мл*	108 [85; 134]	163 [117; 190]	<0.001
Platelet serotonin, ng/mL *Тромбоцитарный серотонин, нг/мл*	84.1 [74.6; 93.2]	74.0 [62.7; 94.2]	0.113
Plasma serotonin/kynurenine *Серотонин плазмы/кинуренин*	1.49 [0.92; 2.15]	3.64 [2.46; 4.41]	<0.001

Note: *FC — functional constipation; IL-1β — interleukin-1β; BDNF — brain-derived neurotrophic factor.*
Примечание: *ФЗ — функциональный запор; IL-1β — интерлейкин-1β; BDNF (brain-derived neurotrophic factor) — нейротрофический фактор головного мозга.*

Table 2. Quality of life, psychoemotional status, and cognitive function in women with functional constipation and healthy women

Таблица 2. Показатели качества жизни, психоэмоционального статуса и когнитивной функции у пациенток с функциональным запором и клинически здоровых женщин

Parameter ***Показатель***	**Patients with FC** ***Пациентки с ФЗ***	**Control group** ***Контрольная группа***	***p***
SF-36 — Physical Functioning *SF-36 — Физическое функционирование*	90.00 [83; 95]	95.00 [95; 95]	<0.001
SF-36 — Role-Physical Functioning *SF-36 — Ролевое функционирование, обусловленное физическим состоянием*	65 [45; 85]	50 [27; 85]	0.332
SF-36 — Bodily pain *SF-36 — Телесная боль*	60 [50; 70]	75 [56; 85]	0.001
SF-36 — General Health *SF-36 — Общее здоровье*	60 [50; 70]	60 [55; 70]	0.764
SF-36 — Vitality *SF-36 — Жизнеспособность*	55 [45; 65]	45 [40; 55]	0.011
SF-36 — Social Functioning *SF-36 — Социальная активность*	75 [70; 86]	75 [60; 85]	0.633
SF-36 — Emotional Wellbeing *SF-36 — Эмоциональное состояние*	67 [33; 89]	67 [41; 93]	0.537
SF-36 — Mental Health *SF-36 — Психическое здоровье*	65 [56; 72]	65 [49; 70]	0.403
HDRS	8 [6; 9]	3 [2; 3]	<0.001
State Anxiety *Ситуативная тревожность*	47 [42; 49]	45 [43; 46]	0.153
Trait Anxiety *Личностная тревожность*	49 [46; 51]	48 [45; 49]	0.235
4DSQ — Distress *4DSQ — Дистресс*	7 [5; 9]	8 [5; 10]	0.865
4DSQ — Depression *4DSQ — Депрессия*	0 [0; 1]	1 [1; 2]	0.002
4DSQ — Anxiety *4DSQ — Тревога*	2 [1; 3]	2 [1; 4]	0.993
4DSQ — Somatization *4DSQ — Соматизация*	9 [7; 12]	5 [3; 9]	<0.001
BACS — Verbal Memory *BACS — Вербальная память*	51 [46; 56]	58 [56; 60]	<0.001
BACS — Digit sequencing *BACS — Последовательность чисел*	48 [42; 52]	46 [42; 51]	0.961
BACS — Token Motor task *BACS — Двигательный тест с фишками*	54 [49; 57]	57 [51; 62]	0.033
BACS — Verbal fluency *BACS — Семантическая и речевая беглость*	53 [47; 58]	56 [52; 61]	0.320
BACS — Symbol Coding *BACS — Шифровка*	49 [43; 51]	53 [50; 56]	<0.001
BACS — “Tower of London” test *BACS — «Башни Лондона»*	51 [47; 53]	48 [46; 51]	0.139
BACS — Total Score *BACS — Общий балл*	50 [45; 54]	54 [53; 56]	0.001

Note: *FC — functional constipation; SF-36 (The Short Form-36) — a questionnaire used to assess health-related quality of life; HDRS — Hamilton Depression Rating Scale; 4DSQ — Four-Dimensional Symptom Questionnaire; BACS — Brief Assessment of Cognition in Schizophrenia.*

Примечание: *ФЗ — функциональный запор; SF-36 (The Short Form-36) — опросник, используемый для оценки качества жизни, связанного со здоровьем; HDRS (Hamilton Depression Rating Scale) — шкала Гамильтона для оценки выраженности депрессии; 4DSQ (Four-Dimensional Symptom Questionnaire) — четырехмерный опросник для оценки выраженности дистресса, депрессии, тревоги и соматизации; BACS (Brief Assessment of Cognition in Schizophrenia) — шкала краткой оценки когнитивных функций при шизофрении.*

Table 3. Gut microbiota taxa significantly different between patients with functional constipation and clinically healthy women (mean number of reads per sample)

Таблица 3. Таксоны кишечной микробиоты, достоверно различающиеся между пациентками с функциональным запором и клинически здоровыми женщинами (среднее количество прочтений в образце)

Taxon ***Таксон***	**Patients with FC** ***Пациентки с ФЗ***	**Control group** ***Контрольная группа***	***p***
Class / *Класс*			
Erysipelotrichia	786.7 [536.6; 1161.9]	292.7 [146.6; 392.4]	<0.001
Bacilli	593.7 [298.4; 1060;0]	115.1 [46.5; 965.7]	<0.05
Order / *Порядок*			
Pasteurellales	3.3 [0.0; 11.9]	0.0 [0.0; 0.0]	<0.05
Erysipelotrichales	786.7 [536.6; 1161.9]	292.7 [146.6; 392.4]	<0.001
Caulobacterales	0.0 [0.0; 0.0]	0.0 [0.0; 1.2]	<0.05
Lactobacillales	575.2 [297.1; 1051.2]	104.0 [43.8; 401.5]	<0.05
Family / *Семейство*			
Ruminococcaceae	11748.1 [9479.4; 14308.8]	17187.0 [15102.7; 18677.7]	<0.0005
Eggerthellaceae	89.4 [48.3; 195.1]	50.8 [15.1; 86.4]	<0.05
Pasteurellaceae	3.3 [0.0; 11.9]	0.0 [0.0; 0.0]	<0.05
Erysipelotrichaceae	786.6 [536.6; 1161.9]	292.7 [146.6; 392.4]	<0.001
Streptococcaceae	407.8 [180.8; 916.8]	83.8 [30.6; 284.4]	<0.05
Caulobacteraceae	0.0 [0.0; 0.0]	0.0 [0.0; 1.2]	<0.05
Genus / *Род*			
Bilophila	21.7 [8.9; 48.4]	59.4 [35.8; 116.0]	<0.05
Alistipes	760.6 [398.0; 1342.1]	1321.2 [1057.7; 1841.0]	<0.05
Faecalibacterium	2561.9 [1634.2; 3945.7]	3703.3 [2863.3; 5911]	<0.05
Haemophilus	2.7 [0.0; 11.9]	0.0 [0.0; 0.0]	<0.05
Megamonas	0.0 [0.0; 0.0]	0.0 [0.0; 0.5]	<0.05
Pseudoflavonifractor	4.8 [0.0; 11.1]	10.5 [7.4; 19.6]	<0.05
Streptococcus	324.9 [109.1; 770.9]	72.7 [22.7; 243.3]	<0.05
Oscillospira	4.8 [0.0; 11.0]	0.0 [0.0; 1.9]	<0.05
Harryflintia	0.0 [0.0; 0.0]	0.0 [0.0; 7.5]	<0.05
Lachnospiraceae NK4B4 group	0.0 [0.0; 0.0]	0.0 [0.0; 3.4]	<0.005
Erysipelotrichaceae UCG-006	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	<0.05
Alcaligenes	0.0 [0.0; 0.0]	0.0 [0.0; 0.1]	<0.005
Brevundimonas	0.0 [0.0; 0.0]	0.0 [0.0; 1.2]	<0.05
Alloscardovia	0.0 [0.0; 0.0]	0.0 [0.0; 0.3]	<0.05
Daeguia	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	<0.05
Species / *Вид*			
Bilophila wadsworthia	7.5 [0.0; 22.4]	38.8 [9.9; 78.0]	<0.05
Bacteroides plebeius	0.0 [0.0; 0.0]	0.0 [0.0; 151.0]	<0.05
Ruminococcus 1 bicirculans	5.5 [0.0; 155.7]	213.2 [85.6; 629.8]	<0.05
Negativibacillus massiliensis	0.0 [0.0; 0.0]	0.0 [0.0; 6.8]	<0.005
Lactococcus raffinolactis	0.0 [0.0; 0.0]	0.0 [0.0; 0.8]	< 0.005
Alloscardovia omnicolens	0.0 [0.0; 0.0]	0.0 [0.0; 0.1]	< 0.005
Coprobacter fastidiosus	0.0 [0.0; 0.0]	0.0 [0.0; 0.6]	< 0.05

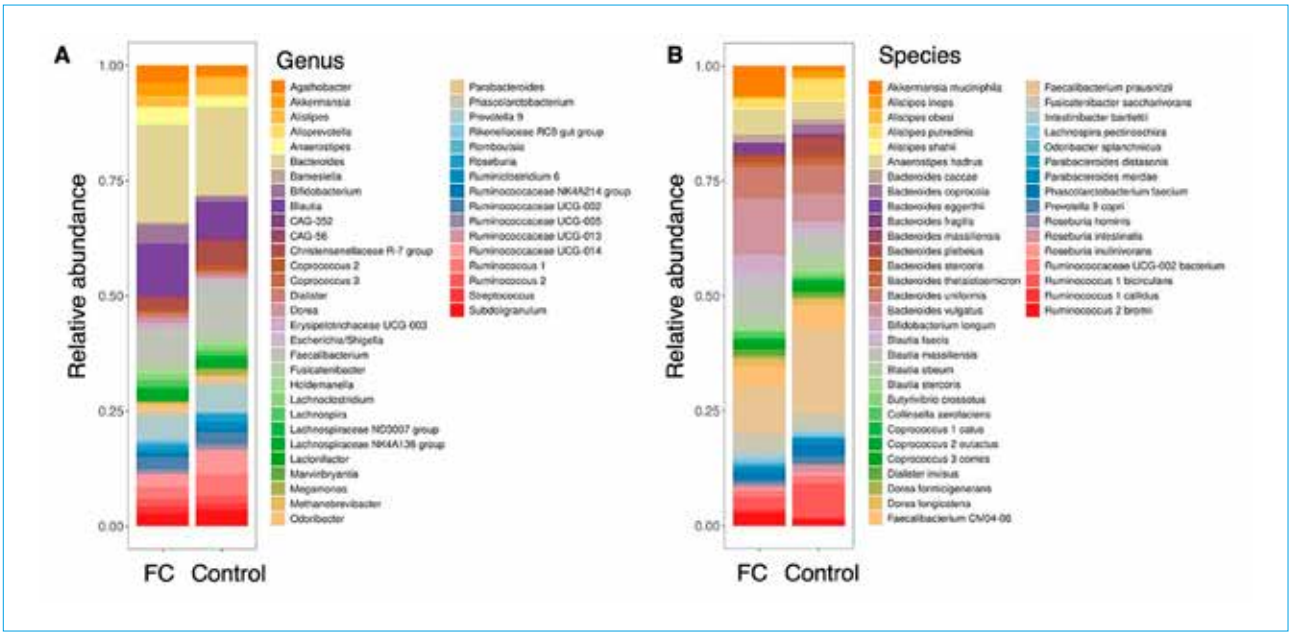

Figure 1. Comparative characteristics of the relative abundance of bacterial taxa at the genus (A) and species (B) levels in patients with FC (left color diagram) and the control group (right color diagram)

Рисунок 1. Сравнительная характеристика относительной численности бактериальных таксонов на уровне рода (A) и вида (B) у пациенток с функциональным запором (левая цветовая диаграмма) и контрольной группы (правая цветовая диаграмма)

Depression severity (HDRS) and somatization (4DSQ) inversely correlated with physical functioning and bodily pain. Depression also inversely correlated with token motor task, while somatization inversely correlated with verbal memory (Table 4). No significant correlations were found between other altered questionnaire indicators.

Cortisol levels positively correlated with bodily pain, while IL-1β levels inversely correlated with bodily pain, physical functioning and verbal memory, and positively correlated with depression and somatization. Plasma

Table 4. Correlations between changed indicators of quality of life, emotional-cognitive status and the severity of depression and somatization among patients with functional constipation

Таблица 4. Корреляции между измененными показателями качества жизни, эмоционально-когнитивного статуса и выраженностью депрессии и соматизации среди пациенток с функциональным запором

	HDRS	**4DSQ — Somatization** ***4DSQ — Соматизация***
SF-36 — Physical Functioning *SF-36 — Физическое функционирование*	$r = -0.270$; $p = 0.032$	$r = -0.309$; $p = 0.013$
SF-36 — Bodily pain *SF-36 — Телесная боль*	$r = -0.615$; $p < 0.000001$	$r = -0.517$; $p = 0.002$
BACS — Verbal Memory *BACS — Вербальная память*	N/S *НЗ*	$r = -0.374$; $p = 0.002$
BACS — Token Motor task *BACS — Двигательный тест с фишками*	$r = -0.258$; $p = 0.038$	N/S *НЗ*

Note: *SF-36 (The Short Form-36) — a questionnaire used to assess health-related quality of life; HDRS — Hamilton Depression Rating Scale; 4DSQ — Four-Dimensional Symptom Questionnaire; BACS — Brief Assessment of Cognition in Schizophrenia; N/S — not significant relationship ($p > 0.05$).*

Примечание: *SF-36 (The Short Form-36) — опросник, используемый для оценки качества жизни, связанного со здоровьем; HDRS (Hamilton Depression Rating Scale) — шкала Гамильтона для оценки выраженности депрессии; 4DSQ (Four-Dimensional Symptom Questionnaire) — четырехмерный опросник для оценки выраженности дистресса, депрессии, тревоги и соматизации; BACS (Brief Assessment of Cognition in Schizophrenia) — шкала краткой оценки когнитивных функций при шизофрении; НЗ — незначимая связь ($p > 0,05$).*

Table 5. Correlations between altered indicators of emotional-cognitive status and quality of life on the one hand and altered biochemical biomarkers on the other among patients with functional constipation

Таблица 5. Корреляции между измененными показателями эмоционально-когнитивного статуса и качества жизни с одной стороны и измененными биохимическими биомаркерами с другой среди пациенток с функциональным запором

	Cortisol ***Кортизол***	**IL-1β**	**Kynurenine** ***Кинуренин***	**Plasma serotonin** ***Серотонин плазмы***	**Plasma serotonin/ kynurenine** ***Серотонин плазмы/ кинуренин***
SF-36 — Physical functioning *SF-36 — Физическое функционирование*	N/S *НЗ*	$r = -0.448$; $p < 0.001$	N/S *НЗ*	$r = -0.259$; $p = 0.042$	$r = -0.259$; $p = 0.041$
SF-36 — Bodily pain *SF-36 — Телесная боль*	$r = 0.379$; $p = 0.003$	$r = -0.391$; $p = 0.002$	N/S *НЗ*	$r = -0.347$; $p = 0.006$	$r = -0.407$; $p = 0.001$
SF-36 — Vitality *SF-36 — Жизнеспособность*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
HDRS	N/S *НЗ*	$r = 0.311$; $p = 0.013$	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
4DSQ — Depression *4DSQ — Депрессия*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
4DSQ — Соматизация *4DSQ — Somatization*	N/S *НЗ*	$r = 0.266$; $p = 0.035$	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
BACS — Вербальная память *BACS — Verbal Memory*	N/S *НЗ*	$r = -0.252$; $p = 0.046$	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
BACS — Token Motor task *BACS — Двигательный тест с фишками*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
BACS — Symbol Coding *BACS — Шифровка*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
BACS — Total Score *BACS — Общий балл*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*

Note: *SF-36 (The Short Form-36) — a questionnaire used to assess health-related quality of life; HDRS — Hamilton Depression Rating Scale; 4DSQ — Four-Dimensional Symptom Questionnaire; BACS — Brief Assessment of Cognition in Schizophrenia; N/S — not significant relationship ($p > 0.05$).*

Примечание: *SF-36 (The Short Form-36) — опросник, используемый для оценки качества жизни, связанного со здоровьем; HDRS (Hamilton Depression Rating Scale) — шкала Гамильтона для оценки выраженности депрессии; 4DSQ (Four-Dimensional Symptom Questionnaire) — четырехмерный опросник для оценки выраженности дистресса, депрессии, тревоги и соматизации; BACS (Brief Assessment of Cognition in Schizophrenia) — шкала краткой оценки когнитивных функций при шизофрении; НЗ — незначимая связь ($p > 0,05$).*

serotonin levels inversely correlated with bodily pain and physical functioning (Table 5).

A correlation was found between the abundance of gut microbiota taxa and blood metabolites in FC patients: cortisol levels showed a positive correlation with *Oscillospira* abundance, kynurenine levels correlated with *Alistipes*, while plasma serotonin levels positively correlated with *Haemophilus* abundance and negatively with *Bacteroides plebeius* (Table 6). No significant associations were found between gut microbiota taxonomic composition and other biomarkers.

Physical functioning correlated with *Lachnospiraceae* NK4B4 group, depression (4DSQ) inversely correlated with *Alistipes* abundance, and Token Motor task (BACS) inversely correlated with *Bacilli*, *Pasteurellales, Lactobacillales, Pasteurellaceae, Streptococcaceae, Haemophilus,* and *Streptococcus* abundance (Table 7). No significant relationship was found between the taxonomic composition of the gut microbiota and the results of other questionnaires.

Discussion

Under normal physiological conditions, approximately 5 % of dietary tryptophan is metabolized into serotonin via TPH-1 and TPH-2 enzymes (the methoxyindole or serotonergic pathway) [10, 11]. The remaining majority is

Table 6. Correlations between significantly different gut microbiota taxa and biochemical biomarkers among patients with functional constipation

Таблица 6. Корреляции между значимо различающимися таксонами кишечной микробиоты и биохимическими биомаркерами среди пациенток с функциональным запором

	Cortisol ***Кортизол***	**IL-1β**	**Kynurenine** ***Кинуренин***	**Plasma serotonin** ***Серотонин плазмы***
Family / *Семейство*				
Erysipelotrichaceae	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
Genus / *Род*				
Alistipes	N/S *НЗ*	НЗ *N/S*	$r = 0.36$; $p = 0.04$	N/S *НЗ*
Haemophilus	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	$r = 0,37$ $p = 0,03$
Oscillospira	$r = 0.45$ $p = 0.01$	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*
Species / *Вид*				
Bacteroides plebeius	N/S *НЗ*	N/S *НЗ*	N/S *НЗ*	$r = -0.40$ $p = 0.02$

Note: *N/S — not significant relationship ($p > 0.05$).*
Примечание: *НЗ — незначимая связь ($p > 0,05$).*

Table 7. Correlations between significantly different gut microbiota taxa and questionnaire data among patients with functional constipation

Таблица 7. Корреляции между значимо различающимися таксонами кишечной микробиоты и данными опросников среди пациенток с функциональным запором

	SF-36 — Physical functioning ***SF-36 — Физическое функционирование***	**4DSQ — Depression** ***4DSQ — Депрессия***	**BACS — Token Motor task** ***BACS — Двигательный тест с фишками***
Class / *Класс*			
Bacilli	N/S *НЗ*	N/S *НЗ*	$r = -0.48$; $p = 0.004$
Order / *Порядок*			
Pasteurellales	N/S *НЗ*	N/S *НЗ*	$r = -0.36$; $p = 0.03$
Lactobacillales	N/S *НЗ*	N/S *НЗ*	$r = -0.48$; $p = 0.004$
Family / *Семейство*			
Pasteurellaceae	N/S *НЗ*	N/S *НЗ*	$r = -0.36$; $p = 0.03$
Streptococcaceae	N/S *НЗ*	N/S *НЗ*	$r = -0.47$; $p = 0.006$
Genus / *Род*			
Alistipes	НЗ *N/S*	$r = -0.37$; $p = 0.03$	N/S *НЗ*
Haemophilus	N/S *НЗ*	N/S *НЗ*	$r = -0.41$; $p = 0.02$
Streptococcus	N/S *НЗ*	N/S *НЗ*	$r = -0.38$; $p = 0.02$
Lachnospiraceae NK4B4 group	$r = 0.35$; $p = 0.04$	N/S *НЗ*	N/S *НЗ*

Note: *SF-36 (The Short Form-36) — a questionnaire used to assess health-related quality of life; 4DSQ — Four-Dimensional Symptom Questionnaire; BACS — Brief Assessment of Cognition in Schizophrenia; N/S — not significant relationship ($p > 0.05$).*
Примечание: *SF-36 (The Short Form-36) — опросник, используемый для оценки качества жизни, связанного со здоровьем; 4DSQ (Four-Dimensional Symptom Questionnaire) — четырехмерный опросник для оценки выраженности дистресса, депрессии, тревоги и соматизации; BACS (Brief Assessment of Cognition in Schizophrenia) — шкала краткой оценки когнитивных функций при шизофрении; НЗ — незначимая связь ($p > 0,05$).*

primarily metabolized through the kynurenine pathway. The synthesized serotonin accumulates in enterochromaffin cells, which release it in response to mechanical and chemical stimuli, thereby serving as sensory transducers that convert these stimuli into neurotransmitter responses [10]. Kynurenine production occurs in the intestines, liver, and brain through the action of tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO) [11]. TDO activity increases in response to elevated circulating cortisol levels, while IDO is stimulated by proinflammatory cytokines (e.g., interferon-gamma, interleukin-1β, interleukin-6, and tumor necrosis factor-alpha) [11]. Kynurenine is subsequently metabolized through two distinct pathways — yielding either quinolinic acid or kynurenic acid, which exert opposing effects on the CNS [11]. Elevated quinolinic acid levels promote neurodegenerative changes in the brain and psychoemotional disorders (anxiety and depression). In contrast, kynurenic acid exhibits neuroprotective properties and counteracts the neurotoxic effects of quinolinic acid [11].

We hypothesized that gut microbiota dysbiosis in FC patients not only shifts tryptophan metabolism toward the kynurenine pathway but also disrupts the "gut — brain" axis homeostasis. This disruption is accompanied by increased levels of circulating proinflammatory cytokines and cortisol. As established, cortisol further stimulates kynurenine production by enhancing TDO activity while simultaneously compromising the integrity of the intestinal mucosal-epithelial barrier. This predisposes to bacterial translocation, thereby amplifying systemic proinflammatory cytokine levels [11, 12]. Additionally, cortisol suppresses the activity of enteric nervous system (ENS) neurons and reduces the excitability of enterochromaffin cells and interstitial cells of Cajal, which serve as pacemakers coordinating colonic peristalsis [12]. Thus, cortisol completes a vicious cycle of neural and hormonal interactions between the CNS and ENS that collectively contribute to slowed colonic motility.

Our findings revealed that FC female patients had elevated kynurenine levels and reduced plasma serotonin, along with a decreased plasma serotonin-to-kynurenine ratio, confirming our hypothesis of tryptophan metabolism shifting toward the kynurenine pathway in FC pathogenesis. Notably, platelet serotonin, tryptophan, and kynurenic acid levels showed no significant differences between groups. The lack of variation in kynurenic acid levels suggests that kynurenine metabolism in FC patients preferentially leads to quinolinic acid formation, though this hypothesis requires further validation. Supporting this notion, C. Chojnacki et al. (2023) demonstrated elevated urinary excretion of kynurenine and quinolinic acid — but not kynurenic acid — in constipation-predominant IBS patients [13]. The correlation analysis did not reveal significant associations between tryptophan, serotonin, or kynurenine levels and the development of psychoemotional or cognitive impairments in the studied cohort.

FC female patients also exhibited elevated blood cortisol and the systemic inflammation marker IL-1β. Interestingly, cortisol increased pain threshold, while IL-1β negatively impacted bodily pain. The direct correlation between cortisol levels and bodily pain explains the aforementioned inverse relationship between plasma serotonin and bodily pain, as cortisol inhibits serotonin synthesis from tryptophan. Furthermore, the higher cortisol levels in the study group may indicate greater emotional lability and lower stress resilience among patients. Given the direct link between cortisol levels and bodily pain, we propose that bodily pain measures may reflect developing somatization processes and reduced stress resilience.

It can be hypothesized that IL-1β serves as a key metabolite that indirectly reduces satisfaction with physical aspects of life in FC patients by exacerbating depression and somatization. The association between elevated IL-1β levels and impaired verbal memory in FC patients may be explained by its direct effects on the CNS. Increased IL-1β is associated with inflammatory changes in brain neurons, leading to impaired dendrite formation and reduced complexity, axonal hypomyelination, and suppression of glutamatergic and cholinergic neurotransmission between brain neurons [14]. IL-1β-induced inflammation in the hippocampus disrupts memory formation and consolidation, manifestations of which we observed in FC patients [14]. In contrast, brain-derived neurotrophic factor (BDNF) promotes neuronal development, maintains their survival, structural integrity and plasticity, and regulates

interneuronal communication and long-term potentiation, thereby supporting long-term memory formation [14]. The absence of significant BDNF differences between study groups suggests that elevated IL-1β, rather than reduced BDNF, plays the pivotal role in verbal memory impairment in FC.

Analysis of emotional health indicators in FC patients revealed differential depression severity - higher levels (mild disorder) were detected using the Hamilton Rating Scale for Depression (HDRS) interview, but not with the self-reported 4DSQ questionnaire, where both groups fell within normal ranges. The HDRS interview is considered the "gold standard" for assessing depressive disorders and is more effective as a screening tool in research settings [15]. Thus, we conclude that while depression is prevalent among FC patients, its presence and severity cannot be reliably identified through self-report questionnaires (including 4DSQ). We also found associations between depression severity (HDRS) and lower thresholds for physical activity and bodily pain, as well as reduced information processing speed.

An important component of this study was the assessment of cognitive health indicators, which revealed decreased overall cognitive abilities in FC patients. It was found that FC particularly reduces verbal memory and information processing speed, while executive functions (planning) and working memory remain unchanged.

Despite high self-rated vitality scores, FC significantly limits patients' physical activity and bodily pain. These indicators relate to the physical health component, meaning patients' daily activities are constrained by negative bodily sensations. Notably, FC patients showed greater somatization tendencies (per 4DSQ self-report questionnaire), which reduced their satisfaction with life aspects. Thus, assessing somatization severity and objective depression evaluation are important indicators when analyzing pain intensity in clinical practice.

We identified numerous bacterial taxa in the gut microbiota that differed between FC patients and healthy women. These changes were observed at class, order, family, genus and species levels. The most significantly reduced taxa in FC patients included bacteria of the *Ruminococcaceae* family, *Faecalibacterium* genus, and *Ruminococcus bicirculans* species, known for their ability to synthesize short-chain fatty acids (SCFAs) and convert primary bile acids into secondary ones [16]. These microbial-derived molecules play a key role in maintaining proper colonic motility [6, 7, 16].

A study in germ-free mice demonstrated that direct administration of SCFAs (acetate and butyrate) into the colon enhanced TPH-1 activity, increasing serotonin levels in the colon and restoring colonic transit in the animals [17]. Additionally, SCFAs exert anti-inflammatory effects by suppressing neutrophil chemotaxis and stimulating the production of anti-inflammatory cytokines (e.g., IL-4 and IL-10) by macrophages, dendritic cells, and lymphocytes in the colon [18]. SCFAs also inhibit nuclear factor kappa B (NF-κB) activity, which induces the synthesis of proinflammatory cytokines TNF-α, IL-1β, and IL-6 by colonic and brain macrophages [18]. Another critical function of SCFAs (particularly butyrate) is maintaining the integrity of the mucosal-epithelial barrier by upregulating tight junction proteins in colonocytes and providing trophic support [17–19]. SCFAs can enter systemic circulation from the colon and cross the blood-brain barrier, directly influencing neurons and microglia through similar mechanisms [19, 20]. Rodent studies have shown that low SCFA levels in various brain structures (including the hippocampus) are associated with increased neuronal inflammation (due to elevated IL-1β and NF-κB activity) as well as the development of depressive disorders and cognitive impairments [20].

Secondary bile acids (particularly deoxycholic and lithocholic acids) enhance colonic transit by stimulating serotonin synthesis and release through activation of the TGR5 bile acid receptor on enteric nervous system neurons and enterochromaffin cells [21]. These bile acids also promote anti-inflammatory immune responses via interactions with both TGR5 and the farnesoid X receptor (FXR) expressed on dendritic cells, macrophages, and regulatory T-cells in the colonic mucosa [16, 21].

Current evidence demonstrates that reduced abundance of *Ruminococcaceae* in the gut microbiota is associated with impaired cognitive function and increased systemic inflammation [22]. Similarly, decreased abundance

of *Faecalibacterium* correlates with elevated systemic inflammatory markers, poorer physical health, and the development of depressive symptoms [23]. Rodent studies have shown that diminished *Alistipes* abundance — as observed in our patient cohort — negatively impacts colonic contractility, although the precise mechanisms underlying this effect remain to be elucidated [10].

Among the elevated gut microbiota taxa in FC patients, notable findings include bacteria from classes *Erysipelotrichia* and *Bacilli*, orders *Erysipelotrichales* and *Lactobacillales*, families *Erysipelotrichaceae* and *Streptococcaceae*, genera *Streptococcus* and *Oscillospira*. *Erysipelotrichaceae* (comprising class *Erysipelotrichia* and order *Erysipelotrichales*) enhance proinflammatory responses, though available data remain limited [19, 24]. For instance, HIV patients demonstrated that *Erysipelotrichia* predominance directly correlated with systemic inflammation severity (serum IL-1β levels) [24]. While *Lactobacillales* (particularly *Lactobacillus*) are traditionally considered beneficial (common in probiotics), their overabundance occurs in irritable bowel syndrome, depression, Parkinson's disease, autism spectrum disorders, rheumatoid arthritis, and ulcerative colitis [19]. Notably, *Lactobacillaceae*, *Streptococcaceae*, and *Streptococcus* exhibit intestinal barrier disruption and bacterial translocation potential [19]. *Oscillospira* (*Firmicutes* phylum, *Clostridia* class) promotes methanogenic archaea growth — strongly associated with excessive methane production that slows colonic motility [25]. These bacteria are more prevalent in female gut microbiota, with their abundance directly correlating with constipation duration and stool consistency [25].

We identified correlative relationships between specific bacterial taxa and biomarker levels involved in FC pathogenesis. However, none of the bacterial taxa showed statistically significant correlations with the investigated biomarkers, suggesting these microbial-indicator relationships may involve more complex interactions. Nevertheless, in female FC patients we observed that increased abundance of class *Bacilli*, orders *Pasteurellales* and *Lactobacillales*, families *Pasteurellaceae* and *Streptococcaceae*, genera *Haemophilus* and *Streptococcus* correlated with impaired information processing speed; elevated

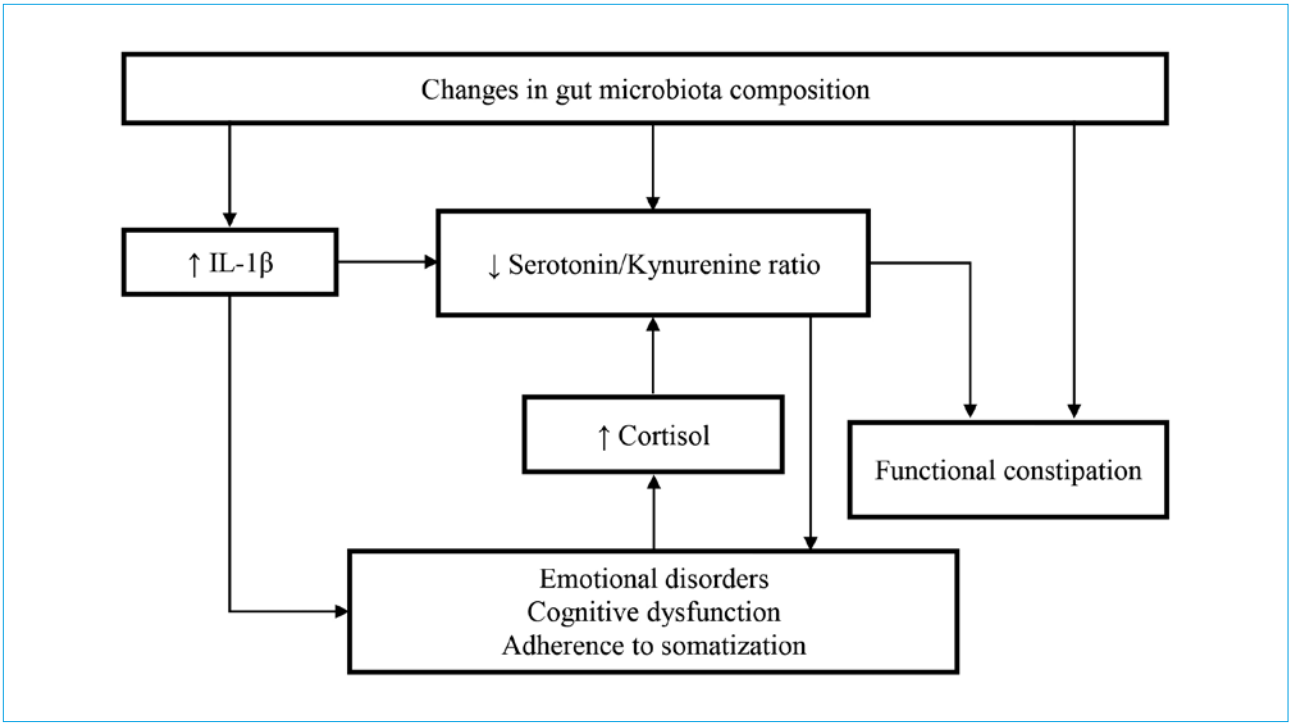

Figure 2. Key pathogenetic mechanisms of development of chronic (functional) constipation with disturbance of the intestinal microbiota composition

Рисунок 2. Ключевые патогенетические механизмы развития хронического (функционального) запора при нарушении состава кишечной микробиоты

Alistipes levels associated with more severe depression (per 4DSQ scores), and reduced *Lachnospiraceae* NK4B4 group abundance positively correlated with quality of life due to physical functioning.

Thus, female patients with FC demonstrate altered gut microbiota composition featuring decreased abundance of bacteria producing SCFAs and secondary bile acids, alongside increased levels of bacteria that suppress colonic motility, promote inflammatory responses, and compromise intestinal barrier integrity. These microbial changes favor tryptophan metabolism shift toward the kynurenine pathway and elevate blood IL-1β levels, which both exacerbates tryptophan metabolic disturbances and contributes to depression and cognitive impairments. The resulting psychoemotional disturbances increase cortisol secretion, which further disrupts tryptophan metabolism. This cascade establishes a vicious cycle that amplifies emotional disorders, cognitive dysfunction, adherence to somatization and FC symptom severity (Fig. 2).

Strengths of the study include the first comprehensive evaluation of key components of the gut-brain axis disruption in FC female patients, encompassing gut microbiota composition analysis, quantification of key metabolites and mediators, assessment of psychoemotional disturbances, cognitive function evaluation and quality of life. This study also provides the first demonstration of altered tryptophan metabolism with detailed blood metabolite profiling in female patients with FC. We further established that FC female patients exhibit depression not detectable by the 4DSQ self-report questionnaire. We also established that FC is associated with distinct cognitive impairment patterns as well as depression and somatization significantly impair quality of life in FC female patients.

Study limitations include small control group size, limited cytokine panel analysis, absence of quinolinic acid measurement. Future research also should investigate small intestinal bacterial overgrowth (including methanogenic organisms) to better understand microbiota's role in tryptophan metabolism dysregulation.

Conclusion

The results indicate that female patients with functional constipation exhibit altered tryptophan metabolism and disrupted gut microbiota composition, which are associated with the development of depression, somatization, cognitive dysfunction, and reduced quality of life due to physical health.

References / Литература

1. *Mearin F., Lacy B.E., Chang L., Chey W.D., Lembo A.J., Simren M., et al.* Bowel disorders. *Gastroenterology*. 2016; S0016-5085(16)00222-5. DOI: 10.1053/j.gastro.2016.02.031
2. *Tomita T., Kazumori K., Baba K., Zhao X., Chen Y., Miwa H.* Impact of chronic constipation on health-related quality of life and work productivity in Japan. *J Gastroenterol Hepatol*. 2021;36(6):1529–37. DOI: 10.1111/jgh.15295
3. *Liang J., Zhao Y., Xi Y., Xiang C., Yong C., Huo J., et al.* Association between depression, anxiety symptoms and gut microbiota in Chinese elderly with functional constipation. *Nutrients*. 2022;14(23):5013. DOI: 10.3390/nu14235013
4. *Salvadori M., Rosso G.* Update on the gut microbiome in health and diseases. *World J Methodol*. 2024;14(1):89196. DOI: 10.5662/wjm.v14.i1.89196
5. *Hou K., Wu Z.X., Chen X.Y., Wang J.Q., Zhang D., Xiao C., et al.* Microbiota in health and diseases. *Signal Transduct Target Ther*. 2022;7(1):135. DOI: 10.1038/s41392-022-00974-4
6. *Cao H., Liu X., An Y., Zhou G., Liu Y., Xu M., et al.* Dysbiosis contributes to chronic constipation development via regulation of serotonin transporter in the intestine. *Sci Rep*. 2017;7(1):10322. DOI: 10.1038/s41598-017-10835-8
7. *Yang C., Hu T., Xue X., Su X., Zhang X., Fan Y., et al.* Multi-omics analysis of fecal microbiota transplantation's impact on functional constipation and comorbid depression and anxiety. *BMC Microbiol*. 2023;23(1):389. DOI: 10.1186/s12866-023-03123-1
8. *Kolobaric A., Andreescu C., Jašarević E., Hong C.H., Roh H.W., Cheong J.Y., et al.* Gut microbiome predicts cognitive function and depressive symptoms in late life. *Mol Psychiatry*. 2024;29(10):3064–75. DOI: 10.1038/s41380-024-02551-3
9. *Ивашкин В.Т., Шелыгин Ю.А., Маев И.В., Шептулин А.А., Алешин Д.В., Ачкасов С.И. и др.* Диагностика и лечение запора у взрослых (Клинические рекомендации Российской гастроэнтерологической ассоциации и Ассоциации колопроктологов России). *Российский журнал гастроэнтерологии, гепатологии, колопроктологии.* 2020;30(6):69–85. [*Ivashkin V.T., Shelygin Yu.A., Maev I.V., Sheptulin A.A., Aleshin D.V., Achkasov S.I., et al.* Clinical Recommendations of the Russian Gastroenterological Association and Association of Coloproctologists of Russia on Diagnosis and Treatment of Constipation in Adults. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2020;30(6):69–85. (In Russ.)]. DOI: 10.22416/1382-4376-2020-30-6-69-85
10. *Waclawiková B., Codutti A., Alim K., El Aidy S.* Gut microbiota-motility interregulation: Insights from in vivo, ex vivo and in silico studies. *Gut Microbes*. 2022;14(1):1997296. DOI: 10.1080/19490976.2021.1997296
11. *Ивашкин В.Т., Фомин В.В., Ткачева О.Н., Медведев О.С., Полуэктова Е.А., Абдулганиева Д.И. и др.* Синдром избыточного бактериального роста в практике врачей различных специальностей (Обзор литературы и резолюция Экспертного совета). *Российский журнал гастроэнтерологии, гепатологии, колопроктологии.* 2024;34(2):14–34. [*Ivashkin V.T., Fomin V.V., Tkacheva O.N., Medvedev O.S., Poluektova E.A., Abdulganieva D.I., et al.* Small intestinal bacterial overgrowth in various specialties of medical practice (literature review

and Expert Council resolution). *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2024;34(2):14–34. (In Russ.)]. DOI: 10.22416/1382-4376-2024-954
12. *Browning K.N., Travagli R.A.* Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. *Compr Physiol*. 2014;4(4):1339–68. DOI: 10.1002/cphy.c130055
13. *Chojnacki C., Błońska A., Konrad P., Chojnacki M., Podogrocki M., Poplawski T.* Changes in tryptophan metabolism on serotonin and kynurenine pathways in patients with irritable bowel syndrome. *Nutrients*. 2023;15(5):1262. DOI: 10.3390/nu15051262
14. *Zhu Q., Wan L., Huang H., Liao Z.* IL-1β, the first piece to the puzzle of sepsis-related cognitive impairment? *Front Neurosci*. 2024;18:1370406. DOI: 10.3389/fnins.2024.1370406
15. *Santi N.S., Biswal S.B., Naik B.N., Sahoo J.P., Rath B.* Comparison of Hamilton Depression Rating Scale and Montgomery-Åsberg Depression Rating Scale: Baked straight from a randomized study. *Cureus*. 2023;15(9):e45098. DOI: 10.7759/cureus.45098
16. *Zhang Y.L., Li Z.J., Gou H.Z., Song X.J., Zhang L.* The gut microbiota-bile acid axis: A potential therapeutic target for liver fibrosis. *Front Cell Infect Microbiol*. 2022;12:945368. DOI: 10.3389/fcimb.2022.945368
17. *Vincent A.D., Wang X.Y., Parsons S.P., Khan W.I., Huizinga J.D.* Abnormal absorptive colonic motor activity in germ-free mice is rectified by butyrate, an effect possibly mediated by mucosal serotonin. *Am J Physiol Gastrointest Liver Physiol*. 2018;315(5):G896–907. DOI: 10.1152/ajpgi.00237.2017
18. *Losol P., Wolska M., Wypych T.P., Yao L., O'Mahony L., Sokolowska M.* A cross talk between microbial metabolites and host immunity: Its relevance for allergic diseases. *Clin Transl Allergy*. 2024;14(2):e12339. DOI: 10.1002/clt2.12339
19. *Maslennikov R., Ivashkin V., Efremova I., Alieva A., Kashuh E., Tsvetaeva E., et al.* Gut dysbiosis is associated with poorer long-term prognosis in cirrhosis. *World J Hepatol*. 2021;13(5):557–70. DOI: 10.4254/wjh.v13.i5.557
20. *Cheng J., Hu H., Ju Y., Liu J., Wang M., Liu B., et al.* Gut microbiota-derived short-chain fatty acids and depression: Deep insight into biological mechanisms and potential applications. *Gen Psychiatr*. 2024;37(1):e101374. DOI: 10.1136/gpsych-2023-101374
21. *Alemi F., Poole D.P., Chiu J., Schoonjans K., Cattaruzza F., Grider J.R., et al.* The receptor TGR5 mediates the prokinetic actions of intestinal bile acids and is required for normal defecation in mice. *Gastroenterology*. 2013;144(1):145–54. DOI: 10.1053/j.gastro.2012.09.055
22. *Oluwagbemigun K., Schnermann M.E., Schmid M., Cryan J.F., Nöthlings U.* A prospective investigation into the association between the gut microbiome composition and cognitive performance among healthy young adults. *Gut Pathog*. 2022;14(1):15. DOI: 10.1186/s13099-022-00487-z
23. *Martín R., Rios-Covian D., Huillet E., Auger S., Khazaal S., Bermúdez-Humarán L.G., et al.* Faecalibacterium: A bacterial genus with promising human health applications. *FEMS Microbiol Rev*. 2023;47(4):fuad039. DOI: 10.1093/femsre/fuad039
24. *Dinh D.M., Volpe G.E., Duffalo C., Bhalchandra S., Tai A.K., Kane A.V., et al.* Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J Infect Dis*. 2015;211(1):19–27. DOI: 10.1093/infdis/jiu409
25. *Chen Y.R., Zheng H.M., Zhang G.X., Chen F.L., Chen L.D., Yang Z.C.* High Oscillospira abundance indicates constipation and low BMI in the Guangdong Gut Microbiome Project. *Sci Rep*. 2020;10(1):9364. DOI: 10.1038/s41598-020-66369-z

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