GUT MICROBIOTA ALTERATIONS IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS

Porosyuk MV, Klementiev DD, Hodov NA, Gumenyuk LN ✉, Esatova ES, Sereda EV, Chetveruhina-Malova KS, Sarchuk EV, Ivanov SV

Georgievsky Medical Academy, Vernadsky Crimean Federal University, Simferopol, Russia

Currently, the issue of the relationship between gut microbiota and juvenile idiopathic arthritis (JIA) is still relevant. The study was aimed to assess alterations in the gut microbiota taxonomic composition and estimate the relationship between these alterations and cortisol, melatonin, and TNFα at the genus level in patients with JIA. The comparative cross-sectional study involved 65 patients with JIA (index group) and 60 healthy children (control group). The gut microbiota taxonomic composition and plasma levels of cortisol, melatonin, and TNFα were assessed. The following alterations of the gut microbiota taxonomic composition were found in patients with JIA: the significantly decreased abundance of *Anaerostipes* (p = 0.042), *Lachnospira* (p = 0.034), Roseburia (p = 0.002), *Coprococcus* (p = 0.014), *Dialister* (p = 0.003) and the increase in the abundance of *Ruminococcus* (p = 0.012). There were significant correlations of cortisol levels with the abundance of *Lachnospira* (r = –0.44; p = 0.001), melatonin concentrations and the abundance of Coprococcus (r = –0.48; p = 0.023), the levels of TNFα and the abundance of *Ruminococcus* (r = 0.52; p = 0.001). The association of the *Lachnospira*, *Roseburia*, and *Ruminococcus* abundance with the higher DAS28 scores was discovered (r = –0.57; p = 0.002; r = –0.44; p = 0.002; r = 0.54; p = 0.032, respectively). The findings provide additional information about the features of gut microbiota alterations and their correlation with some hormone and inflammatory biomarkers associated with JIA, that could provide the basis for further research and possibly for new approaches to treatment of this disorder.

Keywords: juvenile idiopathic arthritis, gut microbiota, cortisol, melatonin, TNFα

Author contribution: Porosyuk MV, Klementiev DD — data acquisition, analysis, and interpretation; Gumenyuk LN — study concept and design; Hodov NA, Esatova ES, Sereda EV — statistical data processing; Chetveruhina-Malova KS, Sarchuk EV, Ivanov SV — manuscript writing

Compliance with ethical standards: the study was approved by the Ethics Committee of the S.I. Georgievsky Medical Academy, V. I. Vernadsky Crimean Federal University (protocol № 10 of 16 November 2020), planned and conducted in accordance with the Declaration of Helsinki. The infirmed consent was submitted by all the subjects enrolled.

✉ **Correspondence should be addressed:** Lesya N. Gumenyuk
Lenina bulvar, 5/7, Simferopol, 295006, Republic of Crimea; lesya_gymenyuk@mail.ru

Received: 01.11.2022 **Accepted:** 29.11.2022 **Published online:** 19.12.2022

DOI: 10.24075/brsmu.2022.060

ИЗМЕНЕНИЯ МИКРОБИОТЫ КИШЕЧНИКА У БОЛЬНЫХ ЮВЕНИЛЬНЫМ ИДИОПАТИЧЕСКИМ АРТРИТОМ

М. В. Поросюк, Д. Д. Клементьев, Н. А. Ходов, Л. Н. Гуменюк ✉, Э. С. Эсатова, Е. В. Середа, К. С. Четверухина-Малова, Е. В. Сарчук, С. В. Иванов

Медицинская академия имени С. И. Георгиевского, Крымский федеральный университет имени В. И. Вернадского, Симферополь, Россия

На сегодняшний день остается актуальной проблема взаимосвязи микробиоты кишечника и ювенильного идиопатического артрита (ЮИА). Целью исследования было изучить изменения таксономического состава микробиоты кишечника и оценить на уровне родов характер их взаимосвязи с кортизолом, мелатонином и TNFα у больных ЮИА. В одномоментном сравнительном исследовании приняли участие 65 больных ЮИА (основная группа) и 60 здоровых детей (контрольная группа). Оценивали таксономический состав микробиоты кишечника, уровни кортизола, мелатонина и TNFα в плазме крови. У больных ЮИА обнаружены изменения таксономического состава микробиоты кишечника: статистически значимое снижение численности *Anaerostipes* (p = 0,042), *Lachnospira* (p = 0,034), *Roseburia* (p = 0,002), *Coprococcus* (p = 0,014), *Dialister* (p = 0,003) и повышение численности *Ruminococcus* (p = 0,012). Установлена статистически значимая корреляция значений кортизола с уровнем бактерий *Lachnospira* (r = –0,44; p = 0,001), концентрации мелатонина и уровнем бактерий *Coprococcus* (r = –0,48; p = 0,023), значений TNFα и уровнем бактерий *Ruminococcus* (r = 0,52; p = 0,001).Также выявлена сопряженность численности бактерий *Lachnospira*, *Roseburia* и *Ruminococcus* с более высокими показателями по DAS28 (r = –0,57; p = 0,002; r = –0,44; p = 0,002; r = 0,54; p = 0,032 соответственно). Результаты предоставляют дополнительные данные об особенностях изменений микробиоты кишечника и их связи с некоторыми гормональными и воспалительными биомаркерами при ЮИА, что может стать обоснованием для проведения дальнейших исследований, а также, возможно, открывает новые подходы к терапии этого заболевания.

Ключевые слова: ювенильный идиопатический артрит, микробиота кишечника, кортизол, мелатонин, TNFα

Вклад авторов: М. В. Поросюк, Д. Д. Клементьев — сбор, анализ и интерпретация данных; Л. Н. Гуменюк — идея и дизайн исследования; Н. А. Ходов, Э. С. Эсатова, Е. В. Середа — статистическая обработка данных; К. С. Четверухина-Малова, Е. В. Сарчук, С. В. Иванов — подготовка статьи.

Соблюдение этических стандартов: исследование одобрено этическим комитетом Крымской медицинской академии имени С. И. Георгиевского ФГАОУ ВО «Крымский федеральный университет им. В. И. Вернадского» (протокол № 10 от 16 ноября 2020 г.), спланировано и проведено в соответствии с Хельсинкской декларацией. Все лица, включенные в исследование, подписали добровольное информированное согласие.

✉ **Для корреспонденции:** Леся Николаевна Гуменюк
бул. Ленина, 5/7, г. Симферополь, 295006, Республика Крым; lesya_gymenyuk@mail.ru

Статья получена: 01.11.2022 **Статья принята к печати:** 29.11.2022 **Опубликована онлайн:** 19.12.2022

DOI: 10.24075/vrgmu.2022.060

Juvenile idiopathic arthritis (JIA) is arthritis of unknown etiology that persists for more than six weeks and occurs in children under the age of 16 [1]. The incidence of JIA all over the world varies between 0.8–22.6 cases per 100,000 children annually, and the prevalence is 7–401 cases per 100,000 children a year [2]. JIA remains one of the vital sociomedical issues due to high prevalence and high levels of early disability [3].

It has been proven that JIA is a multifactorial disease with the complex and poorly understood pathophysiology. In the light of the current concept, aberrant cytokine production along with the dysregulated immune response is a key element of the disease process associated with JIA [4]. In this regard, tumor necrosis factor — (TNFα) that is considered as the “early” cytokine emerging at the onset of inflammatory response [5] and

playing a vital part in the disease process chronification [6], is of special interest. There is evidence that in patients with JIA the levels of TNFα are associated with the activity of inflammation, including cartilage and bone destruction, bone tissue losses [5], while the significantly increased level of TNFα is a predictor of severe complication, the macrophage activation syndrome [5]. Furthermore, the immune system is closely linked with the neuroendocrine system. The pineal-pituitary-adrenal axis deep involvement in the mechanisms underlying the emergence and progression of the JIA clinical symptoms is actively discussed in the literature, and alterations in the melatonin and cortisol secretion are of particular importance [7, 8]. Assessment of blood hormone profiles in patients with JIA revealed the elevated levels of cortisol and the decreased melatonin levels [7, 8]. Moreover, the elevated cortisol levels were related to the clinical markers of inflammation [8], while the levels of melatonin were associated with the process activity, erythrocyte sedimentation rate (ESR), and the levels of immunoglobuline M [8].

Current research suggests that gut microbiota plays a certain role in the development and progression of JIA, resulting from its key role in the neuroendocrine regulation. Thus, the changes in the microbial landscape and disbalance between the members of gut microbiota [9–11], some of which strongly correlate with such biomarkers of inflammation, as anti–cyclic citrullinated peptide antibody, rheumatoid factor, and C-reactive protein [12], are typical for patients with JIA. Furthermore, some microbial representatives are found in the synovial fluid of patients with rheumatoid arthritis [13] and liver tissue of humans and mice [14], which can be the cause of autoimmune reactions [13, 14]. Finally, it was shown that treatment of gut dysbiosis using the specific four-week carbohydrate diet contributed to the decreased plasma levels of TNFα, number of swollen joints, pain syndrome severity, and morning stiffness, as well as to the increased physical activity in patients with JIA [15]. However, many aspects of the relationship between gut microbiota and hormonal biomarkers in patients with JIA are still poorly understood. There is no information about the relationship between the gut microbiota members and the levels of cortisol, melatonin, and TNFα in JIA.

Thus, the issue of the relationship between gut microbiota and JIA is still relevant. The study was aimed to assess alterations in the gut microbiota taxonomic composition and estimate the relationship between these alterations and cortisol, melatonin, and TNFα at the genus level in patients with JIA.

METHODS

The comparative cross-sectional study involved 65 patients with JIA (index group) (39 girls (60.0%), 26 boys (40.0%); average age 10.3 [3.1; 11.6] years), who seeked help in the Children's Outpatient Clinic № 1 and Children's Outpatient Clinic № 3 (Simferopol, Republic of Crimea), and 60 healthy children (control group, CG) (35 girls (58.3%), 25 boys (41.7%); average age 9.9 [3.2; 11.8] years), who underwent their annual medical check-up at the Gemokod medical center (Simferopol, Republic of Crimea) and met the inclusion and exclusion criteria.

Inclusion criteria: first verified case of JIA; child's age 1–16 years; JIA duration 6 weeks to 6 months; no treatment with non-steroidal anti-inflammatory drugs (NSAIDs), genetically engineered biological preparations (GEBPs), and steroids; availability of the parents' informed consent to the child's participation in the study.

Exclusion criteria: systemic JIA, deficit [16] — the criteria for verification of underweight and overweight in children are provided [17]; concomitant somatic diseases; irritable bowel syndrome; chronic disorders of gastrointestinal tract and liver; bacterial, viral, and fungal infections; mental disorders; stool disorders (constipation / diarrhea) within a month before the study; taking antibiotics, probiotics, prebiotics, antivirals, symbiotic or acid–suppression drugs within three months before the study; taking drugs that affect the stool within a month before the study; refusal to participate in the study.

Inclusion criteria for healthy volunteers: age 1–16 years; no chronic disorders or allergy; no more than three respiratory diseases a year; no infectious or acute disorders within two months before the study; no stool disorders (constipation / diarrhea) within a month before the study; refusal to take probiotics, prebiotics, symbiotic drugs within three months before the study; refusal to take drugs that affect the stool within a month before the study; no history of mental disorders; availability of the parents' informed consent to the child's participation in the study.

Exclusion criteria for healthy children: body temperature above 36.9 °C; refusal to participate in the study.

The diagnosis of JIA was verified in accordance with the classification criteria proposed by the International League of Associations for Rheumatology (ILAR), Second Revision (2001) [18]. To provide the disease activity objective assessment, we used the disease activity score (DAS) for 28 joints (DAS28): scores < 2.6 corresponded to remission, 2.6–3.0 to low activity, 3.1–5.0 to moderate avtivity, 5.1 or more to high disease activity [19].

To assess the gut microbiota taxonomic composition, faecal samples were collected in the morning on the day of admission (between 8 am and 11 am), that were frozen and stored in the disposable plastic containers at a temperature of –80 °C until the metagenomic analysis. Total DNA was isolated by the phenol extraction. The fragments of the V3–V4 variable regions of gene encoding 16S rRNA was amplified using universal primers. The V3–V4 region of 16S rRNA of gut microbiota was analyzed in the SOLiD5500 Wildfire sequencer (AppliedBiosystems; USA) by the paired-end sequencing with the total coverage of at least 10,000 pairs of reads per sample [20].

Filtration of the reads based on the quality and taxonomic classification were provided using the QIIME software, v. 1.9.1 [21]. The approach that involved the use of two taxonomic databases was used to define the taxonomic status of the reads. During the first stage we selected the reference set of bacterial operational taxonomic units (OTUs) based on the comparison of the 16S rRNA gene reads obtained with the GreenGenes database, v. 13.5 [22]. During the second phase we defined the taxonomic status of these OTUs based on the HITdb specialized database of human microbiota using the RDP algorithm [23].

The qualitative and quantitative gut microbiota composition was assessed by defining microbial species, genera, and phyla. Assessment of community α-diversity by calculating the Chao1 index, the number of taxa observed (Sobs), and the abundance-based coverage estimator (ACE) was performed using the Mothur software, v.1.22.0 (http:// www.mothur.org).

The serum levels of cortisol, melatonin, and TNFα were assessed by enzyme-linked immunosorbent assay using the test systems (Vector-Best; Russia) and (Immuno Biological Laboratories; Germany). Blood was collected from the cubital vein in the morning (7.00–9.00) after fasting in a resting state (for at least 15 min).

Statistical processing was performed using the STATISTICA 8.0 software package (StatSoft Inc.; USA). When the data were

Table 1. Characteristics of patients with JIA and healthy children

Parameter	Patients with JIA (n = 65)	Control group (n = 60)
Girls/boys, n (%)	39 (60,0)/26 (40,0)	35 (58,3)/25 (41,7)
Average age, years, median [25%; 75%]	10,3 [3,1; 11,6]	9,9 [3,2; 11,8]
Body mass index, kg/m^2, median [25%; 75%]	16,2 [15,1; 18,3]	16,6 [15,7; 18,1]

Table 2. Clinical characteristics of patients with juvenile idiopathic arthritis

Parameter	Patients with JIA (n = 65)
Disease duration, months (M ± CD)	2,5 ± 1,5
Oligoarthritis, n (%)	38 (58,5)
Polyarthritis, n (%)	27 (41,5)
Rheumatoid factor (+), n (%)	8 (12,3)
Anti-CCP (+), n (%)	5(7,7)
Low disease activity based on the DAS28 score, n (%)	49 (75,3)
Moderate disease activity based on the DAS28 score, n (%)	12 (18,5)
High disease activity based on the DAS28 score, n (%)	4 (6,2)
Total DAS28 score, median [25%; 75%]	3,4 [2,9; 4,2]

Note: Anti-CCP — anti–cyclic citrullinated peptide (anti-CCP) antibody

normally distributed, mean values and standard deviations were defined, while in case of non-normal distribution median values, 25th and 75th percentiles were calculated. Distributions were tested for normality using the Gaussian functions. Shares and absolute values were defined for qualitative traits. Comparative analysis of the normally distributed quantitative traits was performed using the parametric Student's t-test, Mann–Whitney U test was used for non-normal distributions, and the chi-squared (χ^2) test was used for qualitative traits. Spearman's rank correlation coefficient was used for assessment of correlations between traits. The correlation analysis and multiple rank correlation analysis were performed, the correlation reliability was tested using the correlation reliability tables. The multiple comparisons were adjusted using the Bonferroni test. The differences were considered significant at $p < 0.05$.

RESULTS

The characteristics of patients with JIA and healthy children are provided in Table 1. The groups were matched for gender ($p = 0.97$; χ^2), age ($p = 0.92$; χ^2), and body mass index ($p = 0.054$; χ^2).

The clinical characteristics of patients with JIA are provided in Table 2. Children with oligoarthritis and low level inflammation prevailed among patients.

Comparison of the gut microbiota taxonomic composition in patients with JIA and children in the CG revealed a significant decrease in the microbial community α-diversity (Chao1 index; $p = 0.017$). The ACE and Sobs indices were slightly decreased in the group of patients with JIA compared to controls, however, there were no significant differences ($p = 0.055$; $p = 0.049$, respectively) (Fig. 1).

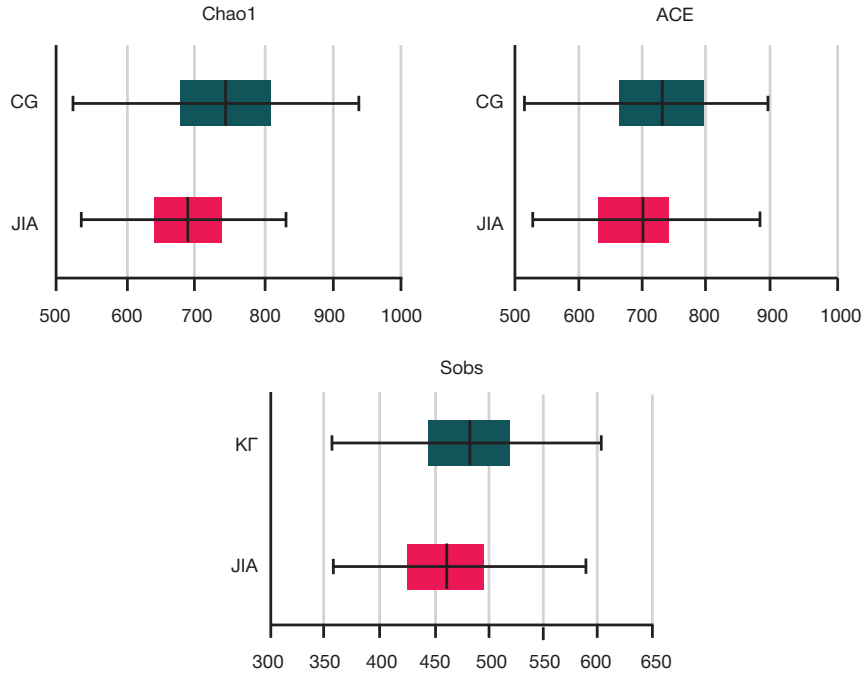

Fig. 1. Comparative analysis of the gut microbiota phylogenetic composition in patients with juvenile idiopathic arthritis and healthy children. JIA — juvenile idiopathic arthritis, CG — control group

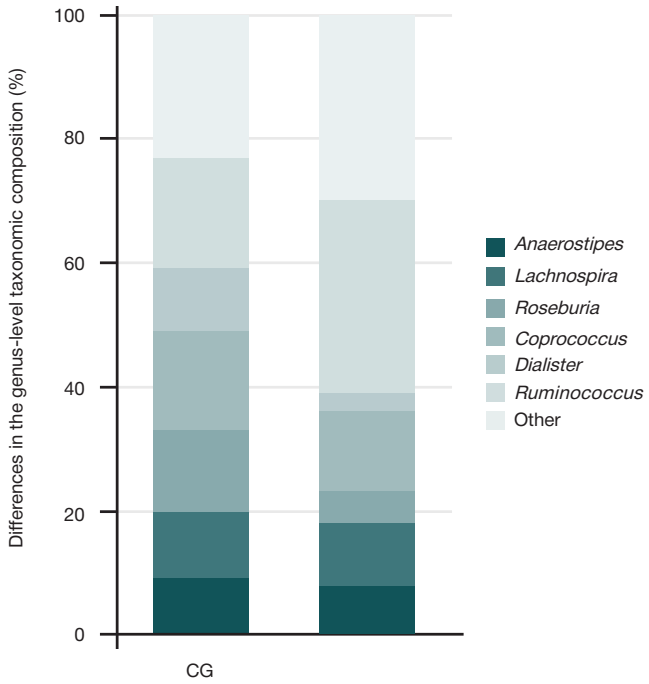

Fig. 2. Comparative analysis of the gut microbiota genus-level taxonomic composition in patients with JIA and healthy children. JIA — juvenile idiopathic arthritis, CG — control group

Comparison of the gut microbiota genus-level taxonomic composition in the surveyed groups revealed that the patients with JIA showed lower abundance of *Anaerostipes* ($p = 0.042$), *Lachnospira* ($p = 0.034$), *Roseburia* ($p = 0.002$), *Coprococcus* ($p = 0.014$), *Dialister* ($p = 0.003$) and higher abundance of *Ruminococcus* ($p < 0.001$) compared to the control group (Fig. 2).

Patients with JIA had the significantly higher plasma levels of cortisol and TNFα and the significantly lower levels of melatonin compared to controls (Table 3).

The cortisol levels and total DAS28 scores strongly correlated with the abundance of *Lachnospira* ($r = –0.44$ at $p = 0.001$; $r = –0.57$ at $p = 0.002$, respectively). We also managed to establish a relationship between the levels of melatonin and the abundance of *Coprococcus* ($r = –0.48$; $p = 0.023$). The correlations of the TNFα levels and total DAS28 scores with the abundance of *Ruminococcus* were established ($r = 0.52$ at $p = 0.001$; $r = 0.54$ at $p = 0.032$, respectively). The total DAS28 scores negatively correlated with the abundance of *Roseburia* ($r = –0.44$; $p = 0.002$).

DISCUSSION

In this study we have clarified alterations in the gut microbiota taxonomic composition and assessed the relationship between these alterations and plasma levels of cortisol, melatonin, and TNFα at the genus level in the group of patients with JIA.

A number of earlier papers report alterations in gut microbiota composition in patients with JIA [9–11]. Our findings also show that the gut microbiota composition of patients with JIA differs significantly from that of healthy children. According to our data, patients with JIA show lower bacterial α-diversity compared to healthy children. This is consistent with the results of the previous studies [9, 10]. Furthermore, dysbiotic alterations of the gut observed in patients with JIA are characterized by the reduced abundance of bacteria having immunomodulatory potential (members of the *Anaerostipes*, *Lachnospira*, *Roseburia*, *Coprococcus*, and *Dialister* genera) that are known to produce the short-chain fatty acids (SCFAs) (butyrate and propionate). The reduced levels of the latter result in activation of histone deacetylase and inhibition of the GPR41, GPR43, and GPR109A G protein coupled receptors, thus promoting chronic inflammation [24]. At the same time, we have discovered high abundance of potential pathobionts, bacteria of the genus *Ruminococcus*. Our findings are partially in line with the number of earlier studies. For example, the decrease in the relative abundance of *Anaerostipes* and *Lachnospira* is typical for patients with JIA [11, 25], however, these data are opposite to the results obtained in patients with rheumatoid arthritis [26]. The other paper reports that the decreased abundance of *Anaerostipes*, *Lachnospira*, and *Roseburia* is typical for patients with COVID-19 [9]. In contrast to our data, the paper [27] reports the increased relative abundance of *Dialister* in patients with JIA. Such conflicting results may be due to the fact that, first, the studies were carried out in different geographic regions, and, second, unlike the abovementioned authors, we included children, who matched patients with JIA for age, gender, and body mass index, in the CG, because the impact of these factors on the gut microbiota composition was proven. Moreover, we did not include the patients with JIA, who used NSAIDs, GEBPs, steroids, and antibacterials in order to neutralize the effects of these drugs on the study results.

Regardless of the fact that some bacteria we have identified can be common for a number of other bowel diseases and systemic disorders, the correlation of the decreased abundance of *Lachnospira* and *Roseburia* and the increased abundance of *Ruminococcus* with the higher DAS28 scores we have discovered suggests that the changes in the abundance of these bacteria may be typical for this cohort of patients with JIA, and may also provide the basis for these alterations to be considered as predictors of the disease progression. The associations revealed were compared with the results of the earlier studies. Thus, in patients with JIA admitted to the hospitals of the Zhejiang Province, the abundance of *Lachnospira* and *Roseburia* negatively correlated with the disease activity, anti-CCP antibody levels, and ESR [9]. Based on the data on the causal relationships between gut dysbiosis and metabolic disorders [28], is can be assumed that the following sequential transformations could be observed in patients with JIA: gut microbiota alterations, specifically, the reduced abundance of bacteria producing SCFAs — the decrease in the concentrations of SCFAs — immune dysfunctions, and eventually the disease. Furthermore, it may be that the therapeutic increase in the abundance of *Lachnospira и Roseburia* and the decrease in the abundance of *Ruminococcus* effectively reduce the disease severity, however, further research with appropriate design is necessary to confirm this hypothesis.

As stated earlier, the patients with JIA show the significantly increased levels of cortisol, melatonin, and TNFα, the role of which in the development and progression of the disease has been proven [7, 8]. Our findings are in line with the literature data: there are significant differences in the levels of cortisol, melatonin, and TNFα between patients with JIA and healthy children. It is worth mentioning, that some gut microbiota representatives found in patients with JIA are associated with plasma levels of the studied biomarkers; this could be indicative of the correlation between the gut microbiota composition and abundance and this disorder. The negative correlation with the plasma cortisol levels have been shown for the genus *Lachnospira*, which confirms the likelihood of these bacteria being actively involved in the hypothalamic-pituitary-adrenal (HPA) axis dysregulation associated with JIA. We have found no studies focused on assessing the relationship between gut microbiota and cortisol in patients with JIA. However, it

Table 3. Comparative analysis of cortisol, melatonin and TNFα levels in blood plasma of patients with JIA and healthy children

Parameter	Patients with JIA (n = 65)	Control group (n = 60)	p
Cortisol, nmol/L ($m \pm CD$)	617,5 ± 17,6	326,1 ± 30,8	$p < 0,001$
Melatonin, pg/mL ($m \pm CD$)	21,1 ± 6,1	35,5 ± 9,2	$p = 0,038$
TNFα, pg/mL ($m \pm CD$)	63,3 ± 1,8	4,6 ± 0,3	$p < 0,001$

Note: p — significance of differences between the JIA group and the control group.

has been reported that *Lachnospira* negatively correlates with cortisol production in healthy children aged 8–16 [29]. Similar data are provided in the paper [30]: the decreased abundance of *Lachnospira* bacteria is associated with the higher cortisol levels in infants. We have found a possible explanation of this relationship in the literature. It is known that *Lachnospira* are among major butyrate-producing bacteria. In turn, SCFAs are capable of affecting the synthesis of cortisol: intracolonic administration of the physiologic doses of SCFAs for seven days resulted in the increased levels of SCFAs in the systemic circulation and reduced cortisol response to acute psychosocial stress in healthy men [31]. It has been found that oral administration of SCFAs (67.5 mmol acetate, 25 mmol propionate, 25 mmol butyrate) for 7 days in mice promoted inhibition of the corticosterone secretion potentiated by acute stress [32]. Since SCFAs are capable of crossing the blood–brain barrier (through the circumventricular organs), it can be assumed that these are involved in modulation of the HPA axis activity via direct effects on the secretory tone in the hypophysiotrophic neurons of the medial parvocellular paraventricular nucleus [33].

The association of melatonin levels with the abundance of *Coprococcus* bacteria has been revealed that can be mediated by blocking signal in the p-CREB-binding protein and arylalkylamine-N-acetyltransferase system due to the decreased secretion of tryptophan [34], being the precursor of serotonin that is subsequently used for synthesis of melatonin. We have found a similar association in patients with type 2 diabetes mellitus in the literature, that is confirmed by positive correlations of the abundance of *Coprococcus* with the levels of tryptophan metabolites and plasma levels of melatonin [35].

A strong positive correlation between the levels of TNFα and the abundance of *Ruminococcus* bacteria suggects that these bacteria play a negative role in the JIA immunogenesis. This could be explained by the following: glucorhamnan, the inflammatory lipopolysaccharide produced by *Ruminococcus* bacteria, induces the synthesis of pro-inflammatory cytokines, such as TNFα and IL6, by the bone marrow dendritic cells through activation of the TLR4-mediated reactions [36].

CONCLUSIONS

The pronounced disorders of the gut microbiota abundance and taxonomic composition have been found in patients with JIA. The discovered significant correlations of some microbiota representatives with the DAS28 scores and the hormonal and inflammatory biomarkers testify in favor of the concept that the gut microbiota abundance and composition are associated with JIA. The issue of the correlation between the gut microbiota alterations and hormone biomarkers is still relevant. The targeted correction of gut microbiota may improve the JIA therapy efficiency.

References

1. Rigante D, Bosco A, Esposito S. The Etiology of Juvenile Idiopathic Arthritis. Clin Rev Allergy Immunol. 2015; 49 (2): 253-61. DOI: 10.1007/s12016-014-8460-9.
2. Shiff NJ, Oen K, Kroeker K, Lix LM. Trends in population-based incidence and prevalence of juvenile idiopathic arthritis in Manitoba, Canada. Arthritis Care Res. 2019; 71 (3): 413–8.
3. Gumenyuk LN, Kabatova IN. Osobennosti kachestva zhizni bol'nyx yuvenil'nym revmatoidnym artritom na sanatorno-kurortnom lechenii. Tavricheskiĭ mediko-biologicheskiĭ vestnik. 2017; 20 (2): 32–35. Russian.
4. Raghavendra VV, Singh AV, Shaji H Vohra, Kulkarni SK, Agrewala JN. Melatonin provides signal 3 to unprimed CD4(+) T cells but failed to stimulate LPS primed B cells. Clin Exp Immunol. 2001; 124: 414–22.
5. Fedorov ES, Salugina SO, Kuzmina NN. Rol' citokinovoj seti v regulyacii vospaleniya pri razlichnyx variantax yuvenil'nogo artrita. 2009; 3: 74–89. Russian.
6. Belyaeva LM, Chizhevskaya ID, Filonovich RM, i dr. Sovremennye podxody k terapii revmaticheskix boleznej u detej. Mezhdunarodnyj zhurnal pediatrii, akusherstva i ginekologii. 2013; 3 (3): 25–34. Russian.
7. Kabatova IN. Sostoyanie gormonal'nogo komponenta adaptacii u deteĭ s yuvenil'nym revmatoidnym artritom. Tavricheskiĭ mediko-biologicheskiĭ vestnik. 2017; 20 (3): 43–48. Russian.
8. Skoromnaya NN. Rol' ehpifizarnogo gormona melatonina v regulyacii razlichnyx zven'ev ehndokrinnoj sistemy u bol'nyx yuvenil'nym revmatoidnym artritom. Zdorov'e rebenka. 2012; 8 (43): 65–70. Russian.
9. Qian X, Liu YX, Ye X, et al. Gut microbiota in children with juvenile idiopathic arthritis: characteristics, biomarker identification, and usefulness in clinical prediction. BMC Genomics. 2020; 21: 286.
10. Di Paola M, Cavalieri D, Albanese D, et al. Alteration of fecal microbiota profiles in juvenile idiopathic arthritis. Associations with HLA-B27 allele and disease status. Front Microbiol. 2016; 7: 1703.
11. Tejesvi MV, Arvonen M, Kangas SM, et al. Faecal microbiome in new-onset juvenile idiopathic arthritis. Eur J Clin Microbiol Infect Dis. 2016; 35 (3): 363–70.
12. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015; 21 (8): 895–905.
13. Pianta A, Arvikar S, Strle K, et al. Evidence of the immune relevance of Prevotella copri, a gut microbe, in patients with rheumatoid arthritis. Arthritis Rheumatol. 2017; 69 (5): 964–75.
14. Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science. 2018; 359 (6380): 1156–61.
15. Berntson L. A pilot study of possible anti-inflammatory effects of the specific carbohydrate diet in children with juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2021; 19 (1): 88.
16. Ashworth A. Nutrition, food security, and health. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. New York: Elsevier, 2015.
17. Gahagan S. Overweight and obesity. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson textbook of pediatrics.

20th ed. New York: Elsevier, 2015; 307–16.
18. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004; 31: 390–2
19. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995; 38: 38–43.
20. Mitra S, Forster-Fromme K, Damms-Machado A,. et al. Analysis of the intestinal microbiota using SOLiD16S rRNA gene sequencing and SOLiD shotgun sequencing. BMC Genomics. 2013; 14 (5): 16.
21. Caporaso JG, Kuczynski J, Stombaugh J, et al. QIIME allows analysis of high-throughput community sequencing data. Nat Methods. 2010; 7 (5): 335–6.
22. DeSantis TZ, Hugenholtz P, Larsen N. Greengenes, a chimera-checked 16S rRNA gene database and workbench compatible with ARB. Appl Environ Microbiol. 2006; 72: 5069–72.
23. Ritari J, Salojärvi J, Lahti L, de Vos WM. Improved taxonomic assignment of human intestinal 16S rRNA sequences by a dedicated reference database. BMC Genomics. 2015; 16 (1): 1056.
24. Vinolo MAR, Rodrigues HG, Nachbar RT, Curi R. Regulation of Inflammation by Short Chain Fatty Acids. Nutrients. 2011; 3 (10): 858–76.
25. Stoll ML, Weiss PF, Weiss JE, et al. Age and fecal microbial strain-specific differences in patients with spondyloarthritis. Arthritis Res Ther. 2018; 20 (1): 14.
26. Breban M, Tap J, Leboime A, et al. Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis. 2017; 76 (9): 1614–22.
27. Tito RY, Cypers H, Joossens M, et al. Brief report: dialister as a microbial marker of disease activity in Spondyloarthritis. Arthritis Rheumatol. 2017; 69 (1): 114–21.
28. Sanna S, van Zuydam NR, Mahajan A, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019; 51 (4): 600–5.
29. Michels N, Van de Wiele T, Fouhy F, et al. Gut microbiome patterns depending on children's psychosocial stress: Reports versus biomarkers. Brain Behav Immun. 2019; 80: 751–62.
30. Rosin S, Xia K, Azcarate-Peril MA, et al. A preliminary study of gut microbiome variation and HPA axis reactivity in healthy infants. Psychoneuroendocrinology. 2021; 124: 105046.
31. Dalile B, Vervliet B, Bergonzelli G, et al. Colon-delivered short-chain fatty acids attenuate the cortisol response to psychosocial stress in healthy men: a randomized, placebo-controlledtrial. Neuropsychopharmacol. 2020; 45: 2257–66.
32. Van de Wouw M, Boehme M, Lyte JM, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain–gut axis alterations. J Appl Physiol. 2018; 596: 4923–44.
33. Ziegler DR, Herman JP. Neurocircuitry of stress integration: anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat1. Integr Comp Biol. 2002; 42: 541–51.
34. Song L, He M, Sun Q, et al. Roseburia hominis Increases Intestinal Melatonin Level by Activating p-CREB-AANAT Pathway. Nutrients. 2022;14:117.
35. Huang X, Qiu Y, Gao Y, et al. Gut microbiota mediate melatonin signalling in association with type 2 diabetes. Diabetologia. 2022; 65 (10): 1627–41.
36. Henke MT, Kenny, DJ, Cassilly CD, et al. Ruminococcus gnavus, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. Proc Natl Acad Sci. 2019; 116: 12672–7.

Литература

1. Rigante D, Bosco A, Esposito S. The Etiology of Juvenile Idiopathic Arthritis. Clin Rev Allergy Immunol. 2015; 49 (2): 253-61. DOI: 10.1007/s12016-014-8460-9.
2. Shiff NJ, Oen K, Kroeker K, Lix LM. Trends in population-based incidence and prevalence of juvenile idiopathic arthritis in Manitoba, Canada. Arthritis Care Res. 2019; 71 (3): 413–8.
3. Гуменюк Л. Н., Кабатова И. Н. Особенности качества жизни больных ювенильным ревматоидным артритом на санаторно-курортном лечении. Таврический медико-биологический вестник. 2017; 20 (2): 32–35.
4. Raghavendra VV, Singh AV, Shaji H Vohra, Kulkarni SK, Agrewala JN. Melatonin provides signal 3 to unprimed CD4(+) T cells but failed to stimulate LPS primed B cells. Clin Exp Immunol. 2001; 124: 414–22.
5. Федоров Е. С., Салугина С. О., Кузьмина Н. Н. Роль цитокиновой сети в регуляции воспаления при различных вариантах ювенильного артрита. 2009; 3: 74–89.
6. Беляева Л. М., Чижевская И. Д., Филонович Р. М. и др. Современные подходы к терапии ревматических болезней у детей. Международный журнал педиатрии, акушерства и гинекологии. 2013; 3 (3): 25–34.
7. Кабатова И. Н. Состояние гормонального компонента адаптации у детей с ювенильным ревматоидным артритом. Таврический медико-биологический вестник. 2017; 20 (3): 43–48.
8. Скоромная Н. Н. Роль эпифизарного гормона мелатонина в регуляции различных звеньев эндокринной системы у больных ювенильным ревматоидным артритом. Здоровье ребенка. 2012; 8 (43): 65–70.
9. Qian X, Liu YX, Ye X, et al. Gut microbiota in children with juvenile idiopathic arthritis: characteristics, biomarker identification, and usefulness in clinical prediction. BMC Genomics. 2020; 21: 286.
10. Di Paola M, Cavalieri D, Albanese D, et al. Alteration of fecal microbiota profiles in juvenile idiopathic arthritis. Associations with HLA-B27 allele and disease status. Front Microbiol. 2016; 7: 1703.
11. Tejesvi MV, Arvonen M, Kangas SM, et al. Faecal microbiome in new-onset juvenile idiopathic arthritis. Eur J Clin Microbiol Infect Dis. 2016; 35 (3): 363–70.
12. Zhang X, Zhang D, Jia H, et al. The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med. 2015; 21 (8): 895–905.
13. Pianta A, Arvikar S, Strle K, et al. Evidence of the immune relevance of Prevotella copri, a gut microbe, in patients with rheumatoid arthritis. Arthritis Rheumatol. 2017; 69 (5): 964–75.
14. Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science. 2018; 359 (6380): 1156–61.
15. Berntson L. A pilot study of possible anti-inflammatory effects of the specific carbohydrate diet in children with juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2021; 19 (1): 88.
16. Ashworth A. Nutrition, food security, and health. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. New York: Elsevier, 2015.
17. Gahagan S. Overweight and obesity. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson textbook of pediatrics. 20th ed. New York: Elsevier, 2015; 307–16.
18. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004; 31: 390–2.
19. Smolen JS, Breedveld FC, Eberl G, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 1995; 38: 38–43.
20. Mitra S, Forster-Fromme K, Damms-Machado A,. et al. Analysis of the intestinal microbiota using SOLiD16S rRNA gene sequencing and SOLiD shotgun sequencing. BMC Genomics. 2013; 14 (5): 16.
21. Caporaso JG, Kuczynski J, Stombaugh J, et al. QIIME allows analysis of high-throughput community sequencing data. Nat Methods. 2010; 7 (5): 335–6.
22. DeSantis TZ, Hugenholtz P, Larsen N. Greengenes, a chimera-checked 16S rRNA gene database and workbench compatible with ARB. Appl Environ Microbiol. 2006; 72: 5069–72.
23. Ritari J, Salojärvi J, Lahti L, de Vos WM. Improved taxonomic assignment of human intestinal 16S rRNA sequences by a

dedicated reference database. BMC Genomics. 2015; 16 (1): 1056.
24. Vinolo MAR, Rodrigues HG, Nachbar RT, Curi R. Regulation of Inflammation by Short Chain Fatty Acids. Nutrients. 2011; 3 (10): 858–76.
25. Stoll ML, Weiss PF, Weiss JE, et al. Age and fecal microbial strain-specific differences in patients with spondyloarthritis. Arthritis Res Ther. 2018; 20 (1): 14.
26. Breban M, Tap J, Leboime A, et al. Faecal microbiota study reveals specific dysbiosis in spondyloarthritis. Ann Rheum Dis. 2017; 76 (9): 1614–22.
27. Tito RY, Cypers H, Joossens M, et al. Brief report: dialister as a microbial marker of disease activity in Spondyloarthritis. Arthritis Rheumatol. 2017; 69 (1): 114–21.
28. Sanna S, van Zuydam NR, Mahajan A, et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. Nat Genet. 2019; 51 (4): 600–5.
29. Michels N, Van de Wiele T, Fouhy F, et al. Gut microbiome patterns depending on children's psychosocial stress: Reports versus biomarkers. Brain Behav Immun. 2019; 80: 751–62.
30. Rosin S, Xia K, Azcarate-Peril MA, et al. A preliminary study of gut microbiome variation and HPA axis reactivity in healthy infants. Psychoneuroendocrinology. 2021; 124: 105046.
31. Dalile B, Vervliet B, Bergonzelli G, et al. Colon-delivered short-chain fatty acids attenuate the cortisol response to psychosocial stress in healthy men: a randomized, placebo-controlledtrial. Neuropsychopharmacol. 2020; 45: 2257–66.
32. Van de Wouw M, Boehme M, Lyte JM, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain–gut axis alterations. J Appl Physiol. 2018; 596: 4923–44.
33. Ziegler DR, Herman JP. Neurocircuitry of stress integration: anatomical pathways regulating the hypothalamo-pituitary-adrenocortical axis of the rat1. Integr Comp Biol. 2002; 42: 541–51.
34. Song L, He M, Sun Q, et al. Roseburia hominis Increases Intestinal Melatonin Level by Activating p-CREB-AANAT Pathway. Nutrients. 2022;14:117.
35. Huang X, Qiu Y, Gao Y, et al. Gut microbiota mediate melatonin signalling in association with type 2 diabetes. Diabetologia. 2022; 65 (10): 1627–41.
36. Henke MT, Kenny, DJ, Cassilly CD, et al. Ruminococcus gnavus, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. Proc Natl Acad Sci. 2019; 116: 12672–7.