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CHARACTERISTICS OF INTESTINAL MICROBIOTA PARAMETERS IN YOUNG PEOPLE WITH METABOLIC SYNDROME

T.S. Dushina*, S.M. Klyashev, L.A. Suplotova, E.F. Dorodneva, M.V. Nikolenko
Tyumen State Medical University, Russian Federation

ХАРАКТЕРИСТИКА ПАРАМЕТРОВ МИКРОБИОТЫ КИШЕЧНИКА У ЛИЦ МОЛОДОГО ВОЗРАСТА С МЕТАБОЛИЧЕСКИМ СИНДРОМОМ

Т.С. Душина*, С.М. Кляшев, Л.А. Суплотова, Е.Ф. Дороднева, М.В. Николенко
Тюменский государственный медицинский университет, Российская Федерация

Objective. To study the features of the colon microbiota, as well as the associations of microbial representatives with anthropometric, anamnestic and biochemical parameters in young patients with metabolic syndrome.
Materials and methods. 118 young people took part in a single-center, one stage, controlled study. 87 of them were diagnosed with obesity, and 31 people with normal body weight formed the control group ("C").

tel. +7 952 341 47 46
e-mail: dr.dushina@mail.ru
[Dushina T.S. (*contact person) – Assistant of the Department of Therapy with Endocrinology, Functional and Ultrasound Diagnostics Courses, ORCID: 0000-0002-6329-593X; Klyashev S.M. – DSc (Medicine), Professor, Head of the Department of Therapy with Endocrinology, Functional and Ultrasound Diagnostics Courses, ORCID: 0000-0001-7739-3859; Suplotova L.A. – DSc (Medicine), Professor of the Department of Therapy with Endocrinology, Functional and Ultrasound Diagnostics Courses, ORCID: 0000-0001-9253-8075; Dorodneva E.F. – DSc (Medicine), Professor of the Department of Faculty Therapy, ORCID: 0000-0001-7203-5729; Nikolenko M.V. – DSc (Biology), Professor of the Department of Microbiology, Head of the Laboratory of Microbiome, Regenerative Medicine and Cell Technology of the University Research Institute of Biomedicine and Medical Biotechnology, ORCID: 0000-0002-1099-0656].

тел.: +7 952 341 47 46
e-mail: dr.dushina@mail.ru
[Душина Т.С. (*контактное лицо) – ассистент кафедры терапии с курсами эндокринологии, функциональной и ультразвуковой диагностики, ORCID: 0000-0002-6329-593X; Кляшев С.М. – доктор медицинских наук, профессор, заведующий кафедрой терапии с курсами эндокринологии, функциональной и ультразвуковой диагностики, ORCID: 0000-0001-7739-3859 ORCID; Суплотова Л.А. – доктор медицинских наук, профессор кафедры терапии с курсами эндокринологии, функциональной и ультразвуковой диагностики, ORCID: 0000-0001-9253-8075; Дороднева Е.Ф – доктор медицинских наук, профессор кафедры факультетской терапии, ORCID: 0000-0001-7203-5729; Николенко М.В. – доктор медицинских наук, профессор кафедры микробиологии, заведующая лабораторией микробиома, регенеративной медицины и клеточных технологии Университетского НИИ биомедицины и медицинской биотехнологии, ORCID: 0000-0002-1099-0656].

87 obese patients were divided into 2 groups: "MS-" which consisted of 43 people (49.4 %), and "MS+" including 44 people (50.6 %) with metabolic syndrome. When stratifying the groups, the NCEP ATP III criteria were used. Blood for biochemical test was taken from all the participants, and the condition of the colon microbiota was assessed using polymerase chain reaction («Colonoflor-16 (premium)»). The Microsoft Excel 2010 and IBM SPSS Statistics 26.0 application software package were used for statistical calculations. The results were evaluated as statistically significant at a level of $p < 0.05$.

Results. In the MS+ group *Fusobacterium nucleatum* (*Fusobacteriaceae* family) was detected statistically significantly more often than in individuals from group "C" (40.5 %). Differences in the bacterial composition of the intestinal microbiota between two groups of obese people were revealed: in the "MS+" group there was a significant decrease in bacteria of the genus *Bifidobacterium* (*Bifidobacteriaceae* family), *Prevotella* (*Prevotellaceae* family) and *Faecalibacterium prausnitzii* (*Ruminococcaceae* family) ($p < 0.05$). In addition, correlation patterns between the species and generic composition of the microbiota on the one hand and age, BMI, waist circumference, hip circumference, breastfeeding duration, indicators of carbohydrate (glucose, insulin, HOMA-IR index) and lipid (total cholesterol, triglycerides, low-density lipoproteins, very low-density lipoproteins, high-density lipoproteins) metabolism, CRP on the other hand have been established.

Conclusions. The colon microbiota in obese patients is characterized by proinflammatory changes. For the metabolically unhealthy phenotype of obesity these changes are most characteristic. It is clear that further research is needed to determine the mechanisms underlying the influence of bacterial-fungal associations on metabolism in obese individuals, as these mechanisms are likely to play a key role in the development of metabolic diseases.

Keywords. Intestinal microbiota, Colonophlor-16 (premium), obesity, metabolic syndrome.

Цель. Изучить особенности микробиоты толстой кишки, а также ассоциации микробных представителей с антропометрическими, анамнестическими и биохимическими параметрами у молодых пациентов с метаболическим синдромом.

Материалы и методы. Проведено одноцентровое, одномоментное, контролируемое исследование с участием 118 молодых людей, из них у 87 человек диагностировано ожирение и у 31 человека нормальная масса тела, которые составляли группу контроля («К»). Из 87 пациентов с ожирением 43 человека (49,4 %) входили в группу «МС-», 44 человека (50,6 %) имели метаболический синдром и составляли группу «МС+». При стратификации групп руководствовались критериями NCEP ATP III. Всем участникам проводился биохимический анализ крови, а также оценка состояния микробиоты толстой кишки методом ПЦР («Колонофлор-16 (премиум)»). Для статистических расчетов был использован пакет прикладных программ Microsoft Exel 2010, IBM SPSS Statistics 26.0. Результаты оценивались как статистически значимые при уровне $p < 0,05$.

Результаты. В группе «МС+», по сравнению с лицами из группы «К», статистически значимо чаще выявляется *Fusobacterium nucleatum* (семейство *Fusobacteriaceae*) (40,5 %). Выявлены различия в бактериальном составе микробиоты кишечника между двумя группами лиц с ожирением, в частности, в группе «МС+» отмечалось достоверное снижение бактерий рода *Bifidobacterium* (семейство *Bifidobacteriaceae*), *Prevotella* (семейство *Prevotellaceae*) и *Faecalibacterium prausnitzii* (семейство *Ruminococcaceae)* ($p \leq 0,05$). Кроме того, установлены корреляционные закономерности между видовым и родовым составом микробиоты, с одной стороны, и возрастом, индексом массы тела, окружностью талии, окружностью бедер, продолжительностью грудного вскармливания, показателями углеводного (глюкоза, инсулин, индекс HOMA-IR) и липидного (общий холестерин, триглицериды, липопротеиды низкой плотности, липопротеиды очень низкой плотности, липопротеиды высокой плотности) обмена, СРБ – с другой.

Выводы. Микробиота толстой кишки у пациентов с ожирением, характеризуется изменениями провоспалительного характера. В наибольшей степени эти изменения свойственны для метаболически нездорового фенотипа ожирения. Очевидно, что необходимы дальнейшие исследования для определения механизмов, лежащих в основе влияния бактериально-грибковых ассоциаций на обмен веществ у лиц с ожирением, поскольку эти механизмы, вероятно, играют ключевую роль в развитии метаболических заболеваний.

Ключевые слова. Микробиота кишечника, «Колонофлор-16 (премиум)», ожирение, метаболический синдром.

INTRODUCTION

The prevalence of obesity and related diseases is increasing worldwide[1]. Obesity is a major risk factor for metabolic diseases. Recently, the concept of "metabolically healthy obesity" (MHO) has been actively used, which means the absence of components of the metabolic syndrome in an obese person [1]. People with MHO are characterized by a lower degree of systemic inflammation, more favorable profiles of the immune system and liver function [2]. However, MHO is a condition that eventually develops into metabolic syndrome (MS). Thus, approximately 30 to 50 % of people with MHO develop "metabolically unhealthy obesity" (MUHO) over a period of 4–20 years [3].

Recently, the theory of the involvement of the intestinal microbiota in the development of obesity and metabolic syndrome has been increasingly discussed. This was initiated by a series of studies conducted by Cani et al. in 2007. The scientists have found that chronic consumption of high-fat diet (HFD) products leads to increased permeability of the intestinal barrier, resulting in higher permeability to byproducts of bacterial metabolism and others antigens, in particular bacterial lipopolysaccharides (LPS), into the systemic circulation with the development of so-called metabolic endotoxemia [4]. Bacterial LPS, activating TLRs (Toll-like receptors), cause an immune response that disturbs insulin sensitivity, and inhibit the normal glycemic response. Thus, the central role of intestinal permeability in chronic low-grade inflammation makes the microbiota a central link in the initiation of metabolic disorders. To date, although we can clearly establish a causal relationship between intestinal microbial profiles and metabolic syndrome in animal experiments, the association between them in the human body does not seem so certain and requires further study. Therefore, further clinical studies are needed to clarify the role of the microbiota in the formation of metabolic disorders, as well as in the prevention and treatment of metabolic syndrome.

The objective of the study was to investigate the features of the colon microbiota, as well as the associations of microbial representatives with anthropometric, anamnestic and biochemical parameters in young patients with metabolic syndrome.

MATERIALS AND METHODS

On the basis of the clinic of Tyumen State Medical University, a single–center, one-stage, cross-sectional, controlled study was conducted with the participation of 118 young people: 87 patients with obesity and 31 patients with a normal body weight who formed the control group ("C"). Obese patients, in turn, were divided into two groups depending on the presence or absence of metabolic syndrome. 43 obese patients (49.4 %) were metabolically healthy and were assigned to the "MS-" group, whereas 44 patients (50.6 %) had metabolic syndrome and were assigned to the "MS+" group. The stratification of the groups was carried out based on the NCEP ATP III criteria.

[1] World Obesity Atlas. World Obesity Federation; 2022, available at: https://www.worldobesity.org/resources/resource-library/world-obesity-atlas-2022

Inclusion criteria for obese patients. Age from 18 to 44 years, signed informed consent, BMI over 30 kg/m^2, absence of somatic pathology.

Inclusion criteria for persons in the control group. Age from 18 to 44 years, signed informed consent, normal body weight (BMI 18.5–24.9 kg/m^2), absence of somatic pathology.

Criteria for non-inclusion. Acute inflammatory diseases during the month before the study, the use of drugs affecting microbial composition and intestinal motility within 3 months before the study, pregnancy/lactation, alcohol abuse.

Each participant was provided with a questionnaire, specially designed in accordance with the objectives of this study. All the participants underwent anthropometric examinations.

The biochemical examination included the determination of total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), triglycerides (TG), glucose levels, C-reactive protein (CRP). The study of biochemical parameters was carried out on the BS-380 Mindray biochemical analyser (China). The level of glycated hemoglobin was determined with the EKF-diagnostic GmbH reagent (Germany) using the Quo-Lab Analyser System (Germany). The insulin level was detected with a set of ELISA reagents manufactured by DRG Techsystems (ЗАО «ДРГ Техсистемс», Russia). All the participants were examined for insulin resistance (HOMA-IR) and evaluation of the functioning of β-cells (HOMA-β). The assessment of the condition of microbiota of the colon was carried out using quantitative real-time polymerase chain reaction (qPCR) with a set of reagents "Colonoflor-16 Premium" by Alfalab LLC ("Колонофлор-16 премиум", ООО «АльфаЛаб», Russia) with fluorescent detection of the results of amplification BioRad CFX96 (USA). The analyses were performed on the basis of the clinical and biochemical laboratory of the Multidisciplinary University Clinic of the Tyumen State Medical University of the Ministry of Health of the Russian Federation (head of the laboratory – Candidate of Medical Sciences N.Yu. Yuzhakova).

This study was conducted in accordance with the protocol approved by the Ethics Committee at the Tyumen State Medical University of the Ministry of Health of the Russian Federation dated March 13, 2023.

For statistical calculations, the Microsoft Excel 2010 and IBM SPSS Statistics 26.0 software was used. The data are presented in the form of median and interquartile range (Me [Q_{25}; Q_{75}]) using the Mann – Whitney and Kruskal–Wallis tests. Spearman's rank correlation method was used to evaluate and identify the associations between variables. The Bonferroni correction was used for multiple comparisons. The results were evaluated as statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

The average age of patients in the "MS-" group was 25 [22; 31] years, in the "MS+" group – 32.5 [25; 40] years ($p = 0.002$). The

average age of the control group was 29 [26; 34] years, which did not significantly differ from the "MS+" and "MS-" groups ($p = 0.310$ and $p = 0.100$, respectively). The study participants in all three groups did not significantly differ in gender. Obese patients in the "MS-" and "MS+" groups did not significantly differ in BMI ($p = 0.848$) waist circumference (WC) (in men, $p = 0.898$, in women, $p = 0.225$), hip circumference (HC) (in men, $p = 0.976$, in women, $p = 0.513$), systolic blood pressure ($p = 0.506$), and diastolic blood pressure ($p = 0.319$), while in comparison with the control group, there were statistically significant differences in all the listed parameters.

According to the level of TC, groups "C", "MS-" and "MS+" had no statistically significant differences ($p = 0.310$). LDL levels did not differ significantly in the "MS-" and "MS+" groups ($p = 0.413$), however, they were statistically higher in the "MS-" ($p = 0.016$) and "MS+" ($p = 0.001$) groups, compared with the "C" group. All three groups differed statistically significantly from each other in terms of VLDL, HDL, TG, as well as the ATG index ($p = <0.001$). Thus, in the patients with a metabolically unhealthy obesity phenotype, the most atherogenic plasma lipid profile was revealed, characterized by a significant increase in LDL cholesterol, VLDL cholesterol, TG and ATG index, as well as a significant decrease in HDL. Glucose levels differed significantly between groups "C" and "MS+" ($p < 0.001$), "MS-" and "MS+" ($p = 0.015$), whereas in groups "C" and "MS-" there were no statistically significant differences ($p = 0.140$). The levels of insulin, calculated HOMA-IR, HOMA-β indices, as well as CRP differed statistically significantly between groups "C" and "MS-" ($p < 0.001$), "C" and "MS+" ($p < 0.001$), while the differences between groups "MS-" and "MS+" were statistically insignificant. However, it is necessary to note a distinct tendency towards the increase of insulin levels, the HOMA-IR index and HbA1c in the "MS+" patients.

When analyzing the intestinal microbiota, differences were found depending on the metabolic status in obese patients (Table). When comparing the microbiota of the "C" and "MS+" groups, it was revealed that *F. nucleatum* (*Fusobacteriaceae* family) was statistically more often found in "MS+" patients (40.5 %), compared with those from the "C" group (10.3 %) ($p = 0.018$). It is known that *Fusobacterium* spp. synthesize a significant amount of butyrate, which is the main source of energy for colonocytes, on the other hand, *F. Nucleatum* is a powerful proinflammatory and protumorogenic agent [5] due to increased secretion of cytokines such as IL-1β, IL-6 and IL-17, increased expression of various TLRs, activation of the STAT3 (signal transducer and activator of transcription 3) signaling pathway, increased proliferation of $CD4^+$ T cells and differentiation into Th-1 and Th-17 [6]. This microorganism is able to disrupt the integrity of the epithelial barrier and increase intestinal permeability by suppressing the expression of the tight junction proteins – zonula occludens-1 (ZO-1) and occludin, which are the markers of the barrier function of the intestinal mucosa. There are differences in the prevalence of *A. mucini-*

phila (family *Akkermansiaceae*) between the groups ($p = 0.013$). Although the differences between groups "C" and "MSMS-" and "MS+" ($p = 0.165$) are unreliable, the statistical significance between groups "C" and "MS+" could not be calculated due to insufficient sampling. However, *A. muciniphila* is an important species capable of maintaining intestinal barrier function, thereby reducing its permeability and translocation of antigenic structures [7]. Therefore, this type of metabolic disorders deserves further study.

When quantifying the number of microorganisms, there was a statistically significant decrease in bacteria of the *Bifidobacterium* genus (*Bifidobacteriaceae* family) ($p = 0.040$) in the "MS+" group. As shown in numerous animal studies, representatives of the genus *Bifidobacterium* have a pronounced anti–inflammatory effect due to their ability to synthesize antibacterial peptides, such as bacteriocins, linoleic acid, acetate.

Animal studies have revealed that the addition of *Bifidobacterium* spp. reduces bacterial translocation, thereby leading to a decrease in endotoxemia and normalization of metabolic parameters [8]. In a randomized, double-blind, placebo-controlled, parallel-group study involving persons with abdominal obesity, Anna Pedret et al. discovered that the intake of *Bifidobacterium Animalis* subsp. led to a decrease in waist circumference (WC), waist circumference to height ratio (WC/H), conicity index (CI), body mass index (BMI) [9]. In the "MS+" group, a statistically significant decrease in another genus of bacteria *Prevotella* (*Prevotellaceae* family) was also found ($p = 0.036$). These bacteria are involved in ensuring the integrity of the intestinal barrier, which is due to their ability to destroy mucins, which make up the mucosal layer surrounding the walls of the digestive tract. At the same time, bacteria of this genus have pro-inflammatory properties realized through the ability to stimulate the production of pro-inflammatory cytokines IL-8, IL-6 by epithelial cells [10].

In the "MS+" patients, the number of *Faecalibacterium prausnitzii* (*F. prau*) ($p = 0.030$) (*Ruminococcaceae* family) was significantly reduced. The number of *F. prau* was also lower in comparison with the control group ($p = 0.006$). As is known, *F.prau* is one of the main butyrate-producing bacteria, which is associated with its pronounced anti-inflammatory properties. In particular, the anti-inflammatory effect was demonstrated in Caco-2 cells in a study in mice with induced colitis by Sokol et al. [11]. Metabolites secreted by *F.prau* blocked the activation of "kappa-bi" nuclear factor (NF-κB) and reduced the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukins IL-12 and IL-8, while stimulating the secretion of anti-inflammatory IL-10. The study by Furet et al. [12] revealed a stable correlation between *F. prau* and chronic inflammation, which demonstrated a negative relationship with serum concentrations of circulating inflammatory markers such as C-reactive protein (CRP) and IL-6. In addition, *F. prau* play an important role in the intestinal barrier integrity

Comparison of quantitative indicators of microbial phylotypes in the feces of healthy people and patients with metabolic health issues (*Me* [Q_1; Q_3])

Phylotypes, quantitative indicators	Control, $n = 31$	"MS-", $n = 43$	"MS+", $n = 44$	p
Total bacterial mass	$1 \cdot 10^{13}$ [$4 \cdot 10^{12}$; $3 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$3 \cdot 10^{12}$; $4 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$2 \cdot 10^{12}$; $4 \cdot 10^{13}$]	0.840
Lactobacillus spp.	$1 \cdot 10^{7}$ [$5 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$9 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$4 \cdot 10^{6}$ [$3 \cdot 10^{5}$; $2 \cdot 10^{7}$]	0.331
Bifidobacterium spp.	$3 \cdot 10^{10}$ [$1 \cdot 10^{9}$; $1 \cdot 10^{11}$]	$2 \cdot 10^{10}$ [$4 \cdot 10^{9}$; $2 \cdot 10^{11}$]	$5 \cdot 10^{9}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	0.022 $p_{C-MS-} = 1.000$ $p_{C-MS+} = 0.078$ $p_{MS-MS+} = 0.040$
Escherichia coli	$2 \cdot 10^{8}$ [$4 \cdot 10^{7}$; $7 \cdot 10^{8}$]	$6 \cdot 10^{8}$ [$1 \cdot 10^{8}$; $2 \cdot 10^{9}$]	$3 \cdot 10^{8}$ [$2 \cdot 10^{7}$; $2 \cdot 10^{9}$]	0.170
Bacteroides spp.	$1 \cdot 10^{13}$ [$4 \cdot 10^{12}$; $2 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$3 \cdot 10^{12}$; $3 \cdot 10^{13}$]	$1 \cdot 10^{13}$ [$2 \cdot 10^{12}$; $3 \cdot 10^{13}$]	0.928
Faecalibacterium prausnitzii	$8 \cdot 10^{11}$ [$1 \cdot 10^{11}$; $2 \cdot 10^{12}$]	$3 \cdot 10^{11}$ [$1 \cdot 10^{11}$; $1 \cdot 10^{12}$]	$9.5 \cdot 10^{10}$ [$7 \cdot 10^{9}$; $4 \cdot 10^{11}$]	0.003 $p_{C-MS-} = 1.000$ $p_{C-MS+} = 0.006$ $p_{MS-MS+} = 0.030$
Eubacterium rectale	$8 \cdot 10^{9}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	$1 \cdot 10^{10}$ [$1.5 \cdot 10^{9}$; $1 \cdot 10^{11}$]	$3 \cdot 10^{9}$ [$8.5 \cdot 10^{7}$; $5 \cdot 10^{10}$]	0.171
Acinetobacter spp.	$8.5 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $3 \cdot 10^{7}$]	$2 \cdot 10^{7}$ [$3 \cdot 10^{6}$; $7 \cdot 10^{7}$]	$6 \cdot 10^{6}$ [$2 \cdot 10^{6}$; $5 \cdot 10^{7}$]	0.294
Roseburia inulinivorans	$7 \cdot 10^{9}$ [$1 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$7 \cdot 10^{9}$ [$5 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$2 \cdot 10^{9}$ [$3 \cdot 10^{7}$; $2 \cdot 10^{10}$]	0.192
Prevotella spp.	$3 \cdot 10^{7}$ [$4 \cdot 10^{6}$; $4 \cdot 10^{10}$]	$3 \cdot 10^{10}$ [$1 \cdot 10^{9}$; $1 \cdot 10^{12}$]	$1 \cdot 10^{9}$ [$4 \cdot 10^{6}$; $2 \cdot 10^{11}$]	0.004 $p_{C-MS-} = 0.006$ $p_{C-MS+} = 0.374$ $p_{MS-MS+} = 0.036$
Bacteroides thetaomicron	$2 \cdot 10^{10}$ [$4 \cdot 10^{8}$; $4 \cdot 10^{10}$]	$7 \cdot 10^{9}$ [$7 \cdot 10^{8}$; $2 \cdot 10^{10}$]	$3 \cdot 10^{9}$ [$2 \cdot 10^{8}$; $2 \cdot 10^{10}$]	0.654
Ruminococcus spp.	$2 \cdot 10^{8}$ [$3.5 \cdot 10^{6}$; $1 \cdot 10^{9}$]	$1.5 \cdot 10^{8}$ [$1 \cdot 10^{7}$; $3.5 \cdot 10^{9}$]	$2 \cdot 10^{8}$ [$9 \cdot 10^{6}$; $3 \cdot 10^{9}$]	0.743
Streptococcus spp.	$6.5 \cdot 10^{6}$ [$4 \cdot 10^{5}$; $4 \cdot 10^{7}$]	$3.5 \cdot 10^{7}$ [$4 \cdot 10^{6}$; $8 \cdot 10^{8}$]	$7 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1 \cdot 10^{8}$]	0.085
Blautia spp.	$2 \cdot 10^{7}$ [$2 \cdot 10^{6}$; $2 \cdot 10^{8}$]	$1 \cdot 10^{8}$ [$6 \cdot 10^{7}$; $2 \cdot 10^{9}$]	$1 \cdot 10^{8}$ [$3 \cdot 10^{7}$; $4 \cdot 10^{9}$]	0.313
Enterobacter spp.	$4 \cdot 10^{7}$ [$4 \cdot 10^{5}$; $2 \cdot 10^{8}$]	$2 \cdot 10^{7}$ [$5 \cdot 10^{6}$; $2 \cdot 10^{8}$]	$5 \cdot 10^{6}$ [$8 \cdot 10^{5}$; $4 \cdot 10^{7}$]	0.424
Staphylococcus aureus	$2.5 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1 \cdot 10^{7}$]	$1.65 \cdot 10^{7}$ [$1.5 \cdot 10^{6}$; $8.5 \cdot 10^{7}$]	$4.5 \cdot 10^{6}$ [$1.5 \cdot 10^{6}$; $8.5 \cdot 10^{6}$]	0.752
Parvimonas micra	$2.5 \cdot 10^{8}$ [$7.5 \cdot 10^{5}$; $4.5 \cdot 10^{16}$]	$3 \cdot 10^{6}$ [$9 \cdot 10^{5}$; $1 \cdot 10^{11}$]	$3 \cdot 10^{6}$ [$1 \cdot 10^{6}$; $1.7 \cdot 10^{8}$]	0.987
Fusobacterium nucleatum	$2 \cdot 10^{5}$ [$2 \cdot 10^{5}$; $7 \cdot 10^{6}$]	$1 \cdot 10^{6}$ [$5 \cdot 10^{5}$; $4 \cdot 10^{6}$]	$8 \cdot 10^{5}$ [$3 \cdot 10^{5}$; $3 \cdot 10^{6}$]	0.578
Escherichia coli enteropathogenic	$1.2 \cdot 10^{4}$ [$4 \cdot 10^{3}$; $2 \cdot 10^{4}$]	$2 \cdot 10^{6}$ [$7 \cdot 10^{5}$; $2 \cdot 10^{6}$]	$3 \cdot 10^{4}$ [$2 \cdot 10^{3}$; $1 \cdot 10^{8}$]	–
Akkermansia muciniphila		$1 \cdot 10^{10}$ [$3 \cdot 10^{6}$; $4 \cdot 10^{10}$]	–	–

system by maintaining tight junction proteins, stimulating ZO-1 expression and proliferation of colon epithelial cells [13].

During the correlation analysis, numerous interrelations of certain microorganisms with anthropometric, biochemical parameters and anamnestic data were revealed. A negative correlation of the total bacterial mass was found (r = -0.336; p = 0.030), *Lactobacillus* spp. (r = -0.365; p = 0.018), *E. coli* (r = -0.310; p = 0.046), *Bacteroides* (r = -0.305; p = 0.050), *Acinetobacter* (r = -0.469; p = 0.002), a positive correlation of *S. aureus* (r = 0.614; p = 0.034) and *P. micra* (r = 0.715; p = 0.046) with age. These data can be considered an indirect confirmation of the hypothesis of a decrease in the diversity and active properties of the microbiota with an increase of patients' age.

The qualitative and quantitative composition of microbiota phyla demonstrated close correlations with anthropometric parameters in obese patients. Thus, positive correlations were found between BMI with *Bifidobacterium* (r = 0.375; p = 0.014), *Bacteroides* (r = 0.310; p = 0.045), *Acinetobacter* (r = 0.342; p = 0.027), and a negative correlation *with F. nucleatum* (r = -0.522; p = 0.031). The value of WC was positively correlated with *Lactobacillus* spp. (r = 0.328; p = 0.034), *Bifidobacterium* spp. (r = 0.412; p = 0.007), a negative correlation was found with *Ruminococcus* spp. (r = -0.387; p = 0.031). The value of HC was positively correlated with the total bacterial mass (r = 0.368; p = 0.017), *Lactobacillus* spp. (r = 0.387; p = 0.011), *Bifidobacterium* spp. (r = 0.443; p = 0,003), *Bacteroides* spp. (r = 0,335; p = 0,030), *B. thetaomicron* (r = 0,359; p = 0,029), *Acinetobacter* spp. (r = 0,388; p = 0,011), *E. rectale* (r = 0,316; p = 0,047).

The decisive role of breastfeeding in shaping the qualitative and quantitative composition of the microbiota was confirmed by the presence of negative correlation dependencies with *Lactobacillus* spp. (r = -0.335; p = 0.035), *B. thetaomicron* (r = -0.356; p = 0.036), and *F. nucleatum* (r = -0.573; p = 0.026). The study also established a positive correlation of *Blautia* spp. with glucose levels (r = 0.419; p = 0.041), *E. rectale* with insulin (r = 0.357; p = 0.024) and the HOMA-IR index (r = 0.343; p = 0.030), as well as *Streptococcus* spp. with the duration of obesity (r = 0.537; p = 0.004).

Significant correlations were found with lipid metabolism indicators: *S. aureus* positively correlated with TG (r = 0.749; p = 0.005), HDL (r = 0.597; p = 0.040), and LDL (r = 0.749; p = 0.005). *M. Smithii* had a positive correlation with HDL (r = 0.810; p = 0.015). Negative correlation dependencies were found for *Acinetobacter* spp. with TC (r = -0.319; p = 0.039) and TG (r = -0.316; p = 0.042), as well as for *Streptococcus* spp. with TC (r = -0.402; p = 0.038). The identified correlation dependencies related to such an important factor characterizing inflammation, as CRP, are also noteworthy. The analysis revealed a positive correlation of CRP with BMI (r = 0.317; p = 0.036), as well as CRP with *Acinetobacter* spp. (r = 0.314; p = 0.043).

CONCLUSION

The microbiota of the large intestine in patients with obesity is characterized by changes of a pro-inflammatory nature. These

changes are most pronounced in the metabolically unhealthy phenotype of obesity. In particular, in the "MS+" group, compared to the "C" group, *F. nucleatum* (*Fusobacteriaceae* family) was statistically more frequently identified (40.5 %). Additionally, in the "MS+" group, compared to the "MS-" group, there was a statistically significant decrease in the bacteria of the genera *Bifidobacterium* (*Bifidobacteriaceae* family) and *Prevotella* (*Prevotellaceae* family). At the species level, the quantity of *F. prau* (*Ruminococcaceae* family) was significantly reduced in the "MS+" group. Correlations were found between representatives of the microbiota and age, BMI, WC, obesity duration, duration of breastfeeding, indicators of carbohydrate metabolism (glucose, insulin, HOMA-IR index), lipid metabolism (TC, TG, LDL, HDL), and CRP.

Clearly, further research is needed to determine the mechanisms underlying the influence of bacterial-fungal associations on metabolism in persons with obesity, as these mechanisms likely play a key role in the development of metabolic diseases.

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