Changes in the gut bacteria composition associated with metabolic syndrome*

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Obesity, arterial hypertension, disorders of carbohydrate and lipid metabolism, which form the metabolic syndrome, remain the leading risk factors for the development of cardiovascular complications and oncological diseases. Overnutrition and a sedentary lifestyle leading to the metabolic syndrome formation are also interconnected with another potential pathogenetic factor of obesity, the gut microbiota. The study of its composition, as well as its metabolites, can serve as a basis for predicting metabolic disorders and for the development of an integrated approach to the metabolic syndrome treatment using probiotic therapy. The clinical assessment of the gut microbiota composition in patients with MS was carried out to identify bacterial taxa potentially associated with the development of MS. Materials (feces) were collected from 113 patients: the first group (n = 59) consisted of overweight patients (body mass index > 25.0) with metabolic disorders in the form of lipid and/or carbohydrate disorders (the average age 44 years). The control group (n = 54) consisted of patients with normal body weight (18.5 < body mass index < 25.0), without metabolic disorders, without arterial hypertension (the average age — 38 years). Fecal samples from patients were studied using 16S rRNA gene sequencing on the Illumina platform (MiSeq sequencer). The CDHIT-OTU-Miseq program was used to search for taxonomic units. Deoxyribonucleic acid libraries were prepared using the Illumina Nextera sample preparation kit with deoxyribonucleic acid primers corresponding to the V3–V4 regions of the 16S rRNA gene. In the gut microbiota composition of patients with metabolic syndrome we can highlight the phylum *Actinobacteria*, its 2 genera *Actynomyces* spp. and *Bifidobacterium* spp., as well as the genus *Prevotella* spp. and the class *Gammaproteobacteria*. It is assumed that bacterial species belonging to these type, class, and genera can be considered as potential marker bacteria of the metabolic syndrome.

Keywords: gut microbiota, metabolic syndrome, obesity, 16s rRNA, *Actinobacteria*, *Bifidobacterium*.

Introduction

Metabolic syndrome (MS) and obesity are the actual problems of modern health care. The prevalence of MS among the adult population averages 25 % [1]. The prevalence of overweight and obesity in the world over the past three decades has increased by almost

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30 and 50 % among adults and children, respectively [2]. By increasing the risk of developing cardiovascular (CVD) and oncological diseases, which are the main cause of death, MS components are important modifiable factors that can affect the prognosis of the disease.

The central link of MS is insulin resistance, a decrease in the sensitivity of peripheral tissues to insulin and hyperinsulinemia, an increase in the mass of visceral fat, the development of disorders of carbohydrate, lipid, purine metabolism, and arterial hypertension [3]. Among the main pathogenic mechanisms of MS, the most interesting is the relationship of insulin resistance with chronic systemic inflammation and endothelial dysfunction. Many methods have been developed to influence these mechanisms, but more and more attention is paid to the role of the gut microbiota in the pathogenesis of metabolic disorders of the whole organism, in the formation and severity of insulin resistance and CVD [4–10].

In a series of experiments, gut flora was transplanted into germ-free mice raised in sterile conditions. As a result, an increase in the adipose tissue mass was observed for 2 weeks by 60 % without any diet changes, which was accompanied by the development of IR, hypertrophy of adipocytes, and increased levels of leptin and blood glucose [11]. In another study, sterile mice got gut flora from lean and obese mice. It turned out that sterile mice that got gutl flora from obese mice gained weight much faster than those that were transplanted with flora from thin counterparts [12]. The obtained data suggested that changes in the gut microbiota may play a role in the pathogenesis of MS and require further study.

Currently, a large number of drugs for correcting the composition of the gut microbiota have been developed. The most used are probiotics (drugs of live cultures microorganisms) and prebiotics (drugs that do not contain live microorganisms, stimulate the growth of their microbiota), as well as their combination in the form of synbiotics. The results of clinical studies indicate that the additional prescription of these drugs as part of complex therapy for obesity is accompanied by an optimization of the qualitative and quantitative gut microbiota composition, a decrease in the severity of carbohydrate and lipid metabolic disorders, an improvement in the outcome and optimization of the terms of patients' treatment [13–15].

Thus, the study of the gut microbiota in patients with MS, its qualitative and quantitative composition, as well as its metabolites is a promising task of modern medicine both for the formation of an effective complex therapy for MS with the use of probiotics and for the creation of a prognostic model regarding the development and progression of this syndrome. In this regard, the aim of our study was the clinical assessment of the gut microbiota composition in patients with MS to identify bacterial taxa potentially associated with the development of MS.

Materials and methods

The work was carried out in the St Petersburg State Budgetary Healthcare Institution "Alexandrovskaya Hospital" and the Department of Faculty Therapy of the Federal State Budgetary Educational Institution "Saint Petersburg State University", where 113 patients were examined. 54 patients constituted a control group of healthy volunteers, 59 patients met the MS criteria according to the national clinical guidelines of 2017, developed by specialists of the Russian Society of Cardiology, the Russian Scientific Medical Society of Therapists, the Antihypertensive League, the Organization for the Promotion of the De-

velopment of Prehospital Medicine "Outpatient Doctor" and the Association of Clinical Pharmacologists [2].

The inclusion criteria in the study group were the age of patients from 25 to 70 years inclusive, informed consent about the participation in the study signed by the patient, central (abdominal) type of obesity, assessed by waist circumference (WC) of more than 80 cm in women and more than 94 cm in men, in combination with two of the following criteria: arterial hypertension (blood pressure (BP) ≥ 130/85 mmHg), increased triglyceride levels (TG ≥ 1.7 mmo/l), decreased high-density lipoprotein cholesterol (HDL cholesterol < 1, 0 mmol/l in men; < 1.2 mmol/l in women), increased levels of low-density lipoprotein cholesterol (LDL cholesterol > 3.0 mmol/l), fasting hyperglycemia (fasting plasma glucose ≥ 6.1 mmol/l), impaired glucose tolerance (plasma glucose 2 hours after glucose loading within ≥ 7.8 and < 11.1 mmol/l).

Exclusion criteria for patients from the study were Itsenko — Cushing's disease, Itsenko — Cushing's syndrome, thyrotoxicosis, hypothyroidism, pheochromocytoma, primary hyperaldosteronism, chronic adrenal insufficiency, ACTH-ectopic syndrome, type 1 diabetes, decompensated type 2 diabetes, decompensated heart failure, ascites as a manifestation of portal hypertension of various etiologies, oncological diseases, organic intestinal pathology, acute infectious and non-infectious diseases, acute intestinal infections in the past six months, alcohol, drug addiction, severe cognitive impairment and mental illness, pregnancy, taking hormonal contraceptives, taking antibacterial drugs, probiotics and prebiotics in the last month, a written refusal to participate in the study.

Healthy volunteers aged 25–70 inclusive, who signed an informed consent about the participation in the study, with normal body weight (BMI = 18.5–24.9 kg/m^2), with BP ≤ 120–129 / 80–84 mmHg, with normal lipid profile and fasting blood glucose constituted the control group.

The clinical examination consisted in studying the history of the disease and the life anamnesis, the patient's complaints to assess compliance with the inclusion criteria and identify exclusion criteria.

Physical examination included an objective examination with BP measurement, anthropometry with WC measurement, and BMI calculation.

Laboratory studies were carried out in the clinical diagnostic laboratory at St Petersburg State Budgetary Health Institution "Municipal Polyclinic № 34". Biochemical analysis of such indicators as blood glucose, HDL, LDL, total cholesterol, and C-reactive protein was performed on the biochemical analyzer ADVIA Chemistry XPT system (Siemens, Germany) and the analyzer Cobas 6000 (ROCHE, Switzerland).

The assessment of the gut microbiota was carried out in the material (feces) from patients of both groups. 2 g of feces were placed in an Eppendorf tube and delivered to the laboratory at the St Petersburg Municipal Polyclinic № 34 no later than 8 hours after the material was collected at ambient temperature. Then, no later than 12 hours after collection, the feces were delivered to the laboratory of biomedical microecology of the Institute of Experimental Medicine, where they were sent frozen at –80 °C and stored until DNA extraction began.

A laboratory study of feces to determine the gut microbiota was carried out at the Institute of Experimental Medicine by the PCR-RT method using the KolonoFlor-16 test system (Alfa Lab, Russia) according to the attached work instructions. The DNA-EXPRESS Bio kit (Alcor Bio, Russia) was used to isolate DNA from feces. Data analysis was performed using a file for processing the results included in the KolonoFlor-16 set.

A selective number of fecal samples, both the control and the main group, were studied using 16S rRNA gene sequencing. In the experiment, sequencing of variable regions V3 and V4 was performed using a MiSeq sequencer (Illumina, USA). Fecal sample preparation was performed according to Illumina protocols using the Illumina Nextera Sample Preparation Kit with DNA primers.

The FAstQC application was used to qualitatively evaluate raw reads. The application allows you to quickly evaluate data errors before carry out further analysis. The CD-HIT-OTU-MiSeq program was used to search for taxonomic units (OTUs), to extract OTUs from paired reads by obtaining clustering results. Clustering was implemented using the following parameters: lengths of high-quality reading areas R1 and R2 read of 200 and 180 bp, respectively, 97 % read similarity for clustering cutoff and 0.00001 for abundance cutoff. OTUs were annotated using the Greengenes database version 13.5 [16].

Statistical analysis

The obtained data were processed using the IBM SPSS Statistics 26 software platform for statistical analysis and the Stattech program. When assessing quantitative traits, the normality of the distribution of the trait was determined using the Kolmogorov — Smirnov criterion. For qualitative traits (changes in the bacterial composition), the absolute value was indicated, as well as the percentage in the structure of the entire population.

Fisher's exact test and Pearson's chi-square test, adjusted for Yates' continuity, were used to describing qualitative signs to assess the significance differences in the frequency of changes in the gut bacteria quantity in the study groups.

To assess the relationship of normally distributed quantitative traits, the Pearson correlation coefficient was used with the determination of the connection closeness according to the Chaddock scale, for abnormally distributed quantitative traits, the Spearman rank correlation coefficient was used, the significance level p of the correlation was determined.

Results

Patients in both groups were comparable in age, sex, and height and differed statistically significantly in body weight, WC, and BMI (Table 1).

Indicators of total cholesterol, fasting blood glucose, CRP in the main and control groups are presented in Table 2. In the control group, the indicators of TG, HDL, LDL were not evaluated due to a large percentage of missing values. When comparing the level of fasting blood glucose and the level of total cholesterol, there is a statistically significantly higher level of fasting blood glucose in the main group compared to patients in the control group ($p = 0.004$).

There were no statistically significant differences in the level of CRP ($p = 0.143$). However, a correlation analysis using the Spearman test between the CRP value, group characteristics and microbiota composition (according to the results of fecal PCR-RT) in both groups revealed a positive moderate correlation ($r = 0.396$, $p = 0.027$) of the CRP level with the amount of *Bifidobacterium* spp. in the control group (Fig. 1).

In addition, a correlation was obtained between the number of *Bifidobacterium* spp. with fasting blood glucose (Spearman's $Po = 0.285$, $p = 0.047$). Statistically significant correlations of CRP levels with other indicators and genera and species of bacteria were not obtained either in the control group or in the main group.

Table 1. **Characteristics of the study groups**

N group	Age. years	Gender	Height. cm	Body weight, kg	Waist circumference, cm	BMI, kg/м^2
1 group (n = 59)	44 (33–49)	♀ 49 % (29 out of 59) ♂ 51 % (30 out of 59)	170 ± 1.6 (95 % CI 167–174)	93* (86.5–107)	104.4 ± 2.4* (95 % CI 99.5–109.4)	32.7 ± 0.8* (95 % CI 31.1–34.3)
2 group (n = 54)	38 (32–48)	♀ 56 % (30 out of 54) ♂ 44 % (24 out of 54)	172 ± 1 (95 % CI 170–174)	63.8* (59–74)	75 ± 1.3* (95 % CI 72.6–77.8)	22.3 ± 0.4* (95 % CI 21.6–23)

Note: CI — confidence interval, * — statistically significant differences between groups ($p < 0.05$).

Table 2. **Comparative characteristics of blood parameters in the examined patients**

Parameter	1st group	2nd group
Cholesterol total, mmol/l	5.5 ± 0.3 (9 5% CI 4.9–6,0)	5.0 (4.5–5.5)
Fasting glucose, mmol/l	5.4* (5.0–6.0)	4.8* (4.4–5.5)
CRP, mg/l	3.2 (1.5–6.7)	2,7 (0.8–4.1)

Note: CI — confidence interval; * — statistically significant differences between groups ($p < 0.05$).

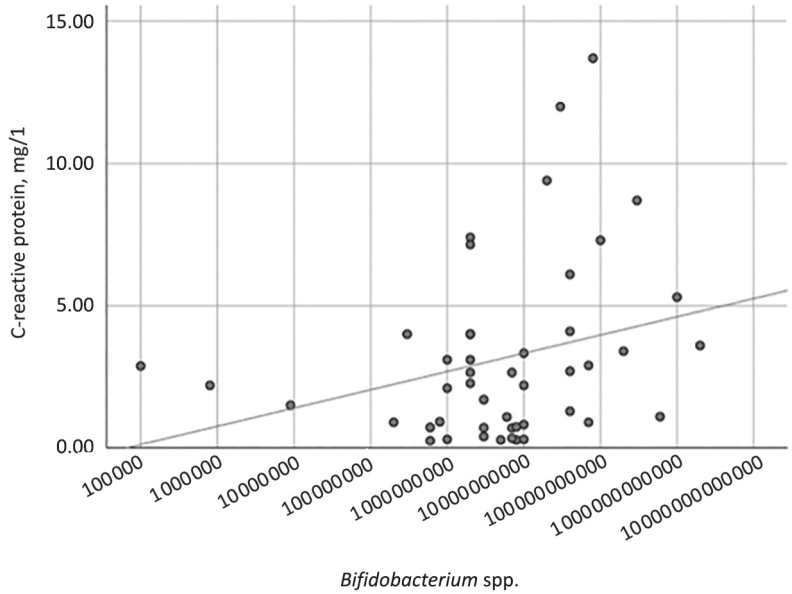

Fig. 1. Relationship between C-reactive protein levels and *Bifidobacterium* spp. ($r = 0.396$, $p = 0.027$)

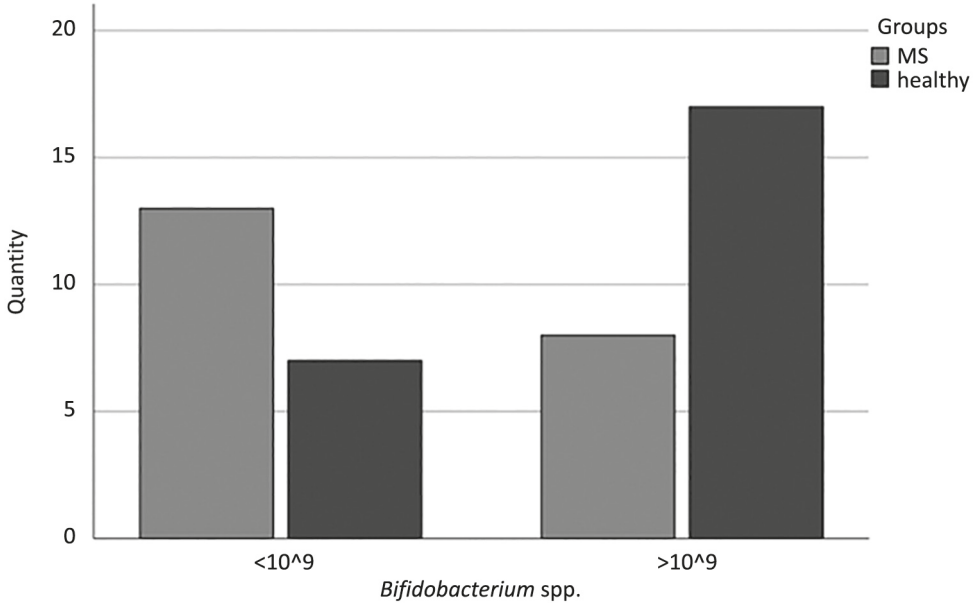

Fig. 2. Difference in *Bifidobacterium* spp. in compared groups (p = 0.038)

PCR-RT Results. The calculation of Fisher's exact test made it possible to identify a statistically significantly more common decrease in the number of *Bifidobacterium* spp. in the group of patients with MS compared with patients in the control group ($p < 0.05$) (Fig. 2). The odds ratio (OR) is 3.946 (95 % CI 1.136–13.708), which means that the chances of a decrease in *Bifidobacterium* spp. in MS is 3.9 times higher than in healthy individuals.

Statistically significant differences between patient groups in terms of total bacterial mass, *Lactobacillus* spp., *Bifidobacterium* spp., *Escherichia coli*, *Bacteroides* spp., *Faecalibacterium prausnitzii, Klebsiella pneumonia, Klebsiella oxytoca, Staphylococcus aureus, Candida* spp., *Clostridium difficile, Clostridium perfringens, Escherichens coli enteropathogenic, Enterococcus* spp., *Bacteroides thetaiotaomicron, Proteus* spp., *Enterobacter* spp./*Citrobacter* spp., *Fusobacterium nucleatum, Parvimonas micra, Akkermansia muciniphila, Bacteroides fragilis* group/*Faecalibacterium prausnitzii* was not obtained ($p > 0.05$).

Results of 16S rRNA gene sequences. When comparing the representation of bacterial taxa, a greater representation of the phylum *Actinobacteria*, the genera *Actynomyces* spp. and *Prevotella* spp. was obtained in the group of patients with MS in comparison with the group of healthy individuals (Figs 3, 4).

Correlations between bacterial taxa, anthropometric parameters, and blood parameters in the group of patients with MS were obtained using correlation analysis according to the Spearman test at a significance level of $p < 0.001$.

In a correlation analysis at the level of bacterial classes, the representation of the *Gammaproteobacteria* class has a strong direct relationship with body weight ($r = 0.8$), BMI ($r = 0.8$), WC ($r = 0.9$) (Fig. 5). There were no correlations between bacterial classes and other indicators at a significance level of $p < 0.001$.

In a correlation analysis at the family level, the representation of *Actinomycetaceae* forms a strong inverse relationship with BMI ($r = –0,7$) and WC ($r = –0,8$) in the MS group.

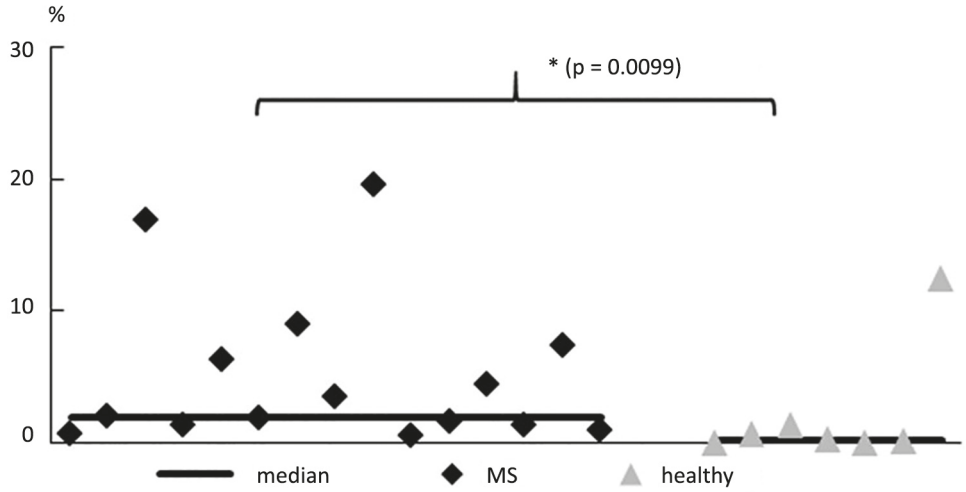

Fig. 3. Representation of the phylum *Actinobacteria* in the studied groups according to the 16S rRNA gene sequencing

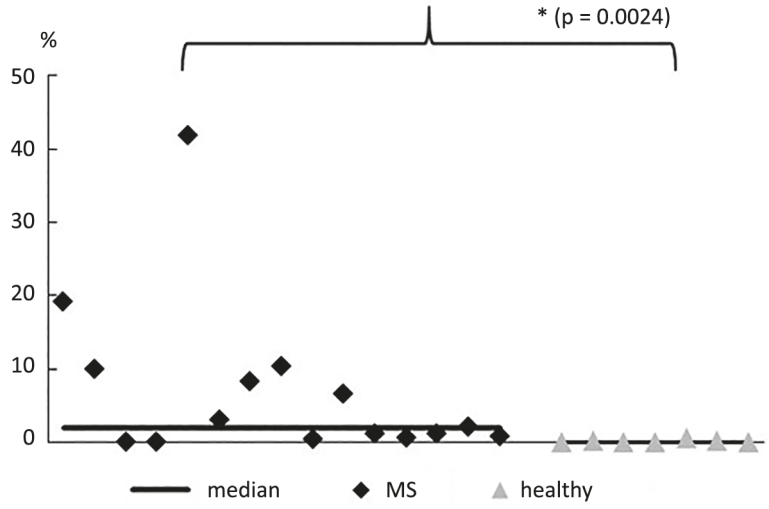

Fig. 4. Representation of the genus *Prevotella* spp. in the study groups according to 16S rRNA gene sequencing

Correlations of bacteria families, as well as phyla, orders, genera of bacteria with other indicators at a significance level of $p < 0.001$ were not established.

Discussion

The aim of this study was to clinically assess the composition of the gut microbiota in patients with MS to identify bacteria taxa that could potentially serve as marker bacteria for MS. According to the results of PCR-RT of feces in the study group, a statistically significantly lower amount of *Bifidobacterium* spp. was revealed compared to the

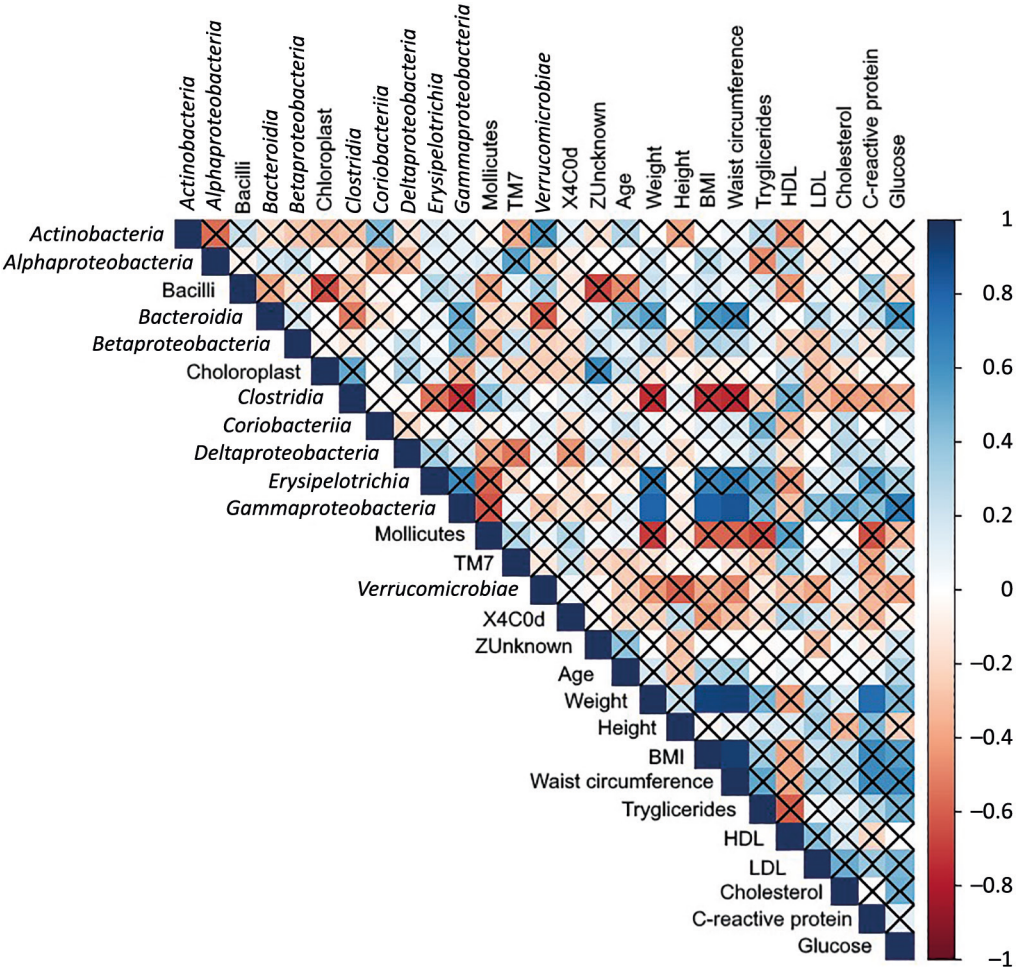

Fig. 5. Corrplot of correlations between bacterial classes, anthropometric parameters and blood parameters in the MS group. Statistically significant correlations ($p < 0.001$) are represented by a square without a cross, the rank correlation coefficient is marked in color (red color — strong inverse relationship, $r = -1$, blue color — strong direct relationship, $r = 1$)

control group. According to the data obtained, the chances of reducing the number of *Bifidobacterium* spp. in MS is 3.9 times higher than in healthy individuals. Similar results were obtained in the work of Cerano C. Da Silva dedicated to studying the gut microbiota by sequencing the 16S rRNA gene in 51 obese children from the island of Tobago. A statistically significantly lower amount of *Bifidobacterium* spp. was found in the group of children with obesity compared with normal body weight children [17]. In a study by M. Kalliomaki, it was found that the representation of bifidobacteria, which affect both the quantity and quality of the microbiota during the first year of life, was higher in children of seven years age with normal weight than in overweight children [18]. Based on the results of this study, it was assumed that the gut microbiota composition determines the formation of metabolic disorders, and also affects the LPS-induced inflammation observed in

obesity. It has been proven that in the presence of butyrate or conjugated linolenic acid-producing by such bacteria, as *Bifidobacteria* or *Lactobacillus*, there is an improvement in glucose tolerance in combination with a decrease in endotoxemia, circulating pro-inflammatory cytokines, and intestinal permeability [19; 20]. However, there is evidence of the primary importance of nutrition and LPS-induced metabolic endotoxemia in reducing the number of *Bifidobacterium* spp., changing the gut microbiota composition, and the development of obesity, metabolic disorders. In a study by Patrice D. Cani, when LPS was administered to mice (C57bl6/J male mice and CD14-mutated male mice derived from C57bl6/J mice) on a carbohydrate-free high-fat diet, a decrease in the representation of *Bifidobacterium* spp. with the formation of obesity and diabetes was found compared with mice with normal nutrition [21].

Thus, whether the identified decrease in the representation of *Bifidobacterium* spp. is a consequence of excess fat intake and the formation of obesity, or primarily to the development of obesity and metabolic disorders, remains an open question. However, this genus of bacteria can be considered to correct MS by taking prebiotics and probiotics that affect the amount of *Bifidobacterium* spp. in the gut microbiota.

Other genera and species of bacteria, assessed by fecal PCR-RT, did not significantly differ between the groups.

In correlation analysis, weak correlations were obtained for the representation of the genus *Bifidobacterium* spp. with the CRP level, as well as with the level of fasting blood glucose in the control group. In the group of patients with MS, these correlations were not obtained. It can be assumed that under conditions of metabolic endotoxemia in MS, *Bifidobacterium* spp. perform a protective role, compensating endotoxemia, the action of pro-inflammatory cytokines, and improving glucose tolerance. In the absence of obesity and associated metabolic disorders *Bifidobacterium* spp. do not fulfill this role due to the lack of excess LPS and dietary fats that affect their quantity and, probably, the bacteria metabolism. In addition, attention should be paid to certain types of bifidobacteria, the ratio of which influences the formation of a positive or negative relationship with lipid panel, carbohydrate metabolism, CRP.

Also, the composition of the gut microbiota was analyzed using the 16S rRNA gene sequencing method. In the MS group, the phylum *Actinobacteria* is statistically significantly more represented than in the control group. The statistically significant difference in the representation of the Actinobacteria phylum obtained in the study is confirmed in the Irish study in 2020, where a larger number of this phylum was also detected in the Landrace pig model with MS than in the control group. In addition, a strong positive correlation has been established between hypertension with dyslipidemia and the amount of the *Actinobacteria phylum* [22]. A similar relative increase of *Actinobacteria* in humans with obesity was noted in studies by Peter Turnbaugh (2009), Manuel Ferrer (2012) [23; 24].

At the genus level, according to sequencing data, the genus *Actinomyces* spp. is more represented in the MS group in comparison with the control group. These changes in the microbiota composition resonate in the 2018 work of Federica del Chierico, where *Actinomyces* were isolated as microbial markers of obesity [25]. However, according to the results of our study, the family *Actinomycetaceae* (it includes the genus *Actinomyces* spp.) forms a strong inverse correlation with BMI and WC in the MS group. Maybe it is necessary to pay attention to other genera of bacteria belonging to this family, which can positively affect lipid and carbohydrate metabolism and explain the inverse obtained correlations.

Along with a large representation of the genus *Actinomyces* spp., according to sequencing data, a greater representation of the genus *Prevotella* spp. was revealed in the MS group in comparison with the control group. In a 2021 Chinese study examining the gut microbiota of 21 obese patients, as well as in our study, there was a greater representation of the genus *Prevotella* spp., as well as the genera *Megamonas*, *Fusobacterium*, and *Blautia*, with a decrease in the number of *Faecalibacterium*, *Clostridium* XIVa [26]. In a Danish randomized clinical trial in 46 overweight volunteers, a higher *Prevotella* spp. representation was associated with greater weight loss on a fiber and whole-grain wheat rich diet compared to a volunteer's group with a lower *Prevotella* spp. representation. The authors confirm the expediency of isolating the *Prevotella*-enterotype as a biomarker for the development of personalized nutrition in the treatment of obesity [27]. Also, in 2020 Korean double-blind, placebo-controlled study investigating the effect of probiotic intake on obesity, *Prevotella* enterotype was associated with the best effect of probiotic therapy (reduction of WC, total fat mass, visceral to subcutaneous fat ratio) in comparison with a Bacteroides-enterotype group [28].

Thus, the genus *Prevotella* spp. can be considered as a genus of bacteria that characterizes the gut microbiota of people with obesity and MS. Isolation of the enterotype with a predominance of *Prevotella* spp. it is advisable both for the development of personalized nutrition in the correction of obesity and for the prognostic evaluation of the effectiveness of probiotic therapy in this category of patients.

Conclusion

Summing up the analysis of the qualitative and quantitative composition of the gut microbiota in MS, we can distinguish the phylum *Actinobacteria*, its 2 genera *Actynomyces* spp. and *Bifidobacterium* spp., as well as the genus *Prevotella* spp. and the class *Gammaproteobacteria*. It is assumed that the ratio of these genera can be considered when assessing metabolic disorders in MS, and bacterial species belonging to a given type, class, and genera can be considered as potential marker bacteria of MS. However, whether this is of prognostic value in relation to the development of MS (under the condition of a primary change in the composition of the gut microbiota under the influence of nutrition, followed by the development of obesity) or whether it reflects the severity of metabolic disorders (if changes in the microbiota composition are due to the formed MS) remains an urgent question.

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Изменения состава кишечной микробиоты при метаболическом синдроме*

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Ожирение, артериальная гипертензия, нарушения углеводного и липидного обмена, формирующие метаболический синдром, остаются ведущими факторами риска развития сердечно-сосудистых осложнений и онкологических заболеваний. Избыточное

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питание и малоподвижный образ жизни, приводящие к формированию метаболического синдрома, также связаны с потенциальным патогенетическим фактором развития ожирения — кишечной микробиотой. Изучение ее состава может способствовать разработке комплексного подхода к лечению метаболического синдрома с применением пробиотической терапии. Целью исследования являлась оценка состава кишечной микробиоты у пациентов с метаболическим синдромом для выявления таксонов бактерий, потенциально ассоциированных с его развитием. Был проанализирован материал пациентов двух групп: первую группу составили 59 пациентов с метаболическим синдромом (средний возраст пациентов — 44 года). Контрольную группу составили 54 пациента с нормальной массой тела без метаболических нарушений и артериальной гипертензии (средний возраст пациентов составил 38 лет). Образцы кала пациентов были исследованы методом секвенирования гена 16s рРНК на платформе Illumina (секвенатор MiSeq). Подготовка образцов фекалий проводилась согласно протоколам Illumina с использованием набора для подготовки образцов Illumina Nextera. Программа CD-HIT-OTU-MiSeq применялась для поиска таксономических единиц. Результаты показали, что в составе микробиоты толстой кишки пациентов с метаболическим синдромом можно выделить тип Actinobacteria, его два рода Actynomyces spp. и Bifidobacterium spp., а также род Prevotella spp. и класс Gammaproteobacteria. Вероятно, виды бактерий, относящиеся к данному типу, классу и родам, можно рассматривать в качестве потенциальных маркерных бактерий метаболического синдрома.

Ключевые слова: кишечная микробиота, метаболический синдром, ожирение, 16S рРНК, Actinobacteria, Bifidobacterium.

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