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ORIGINAL RESEARCHES

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Characteristics of the colonic microbiome in patients with different obesity phenotypes (the original article)

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Abstract

Introduction. The concept of heterogeneity in obesity depending on the risk of developing cardiometabolic complications has garnered attention in recent decades, since not everyone with obesity goes on to develop metabolic dysfunction.

The aim of the work is to study specific characteristics of colonic microbial communities in patients with different obesity phenotypes and in healthy individuals by employing metagenomics methods.

Materials and methods. A total of 265 individuals (44 men and 221 women; mean age 47.1 ± 4.8 years) were enrolled in the study. They were further divided into clinical groups: Healthy normal-weight individuals (n = 129); patients with obesity (n = 136), including metabolically healthy obesity (n = 40) and metabolically unhealthy obesity (n = 55). Quantitative and qualitative assessment of the intestinal microbiome was based on metagenomic analysis. Fecal samples were used to isolate DNA and perform sequencing of the variable v3-v4 region of the *16S* rRNA gene.

Results. The study revealed statistically significant (p < 0.05) differences between quantitative and qualitative variables in studied phylotypes of colonic microorganisms in healthy individuals without obesity and in patients with different obesity phenotypes.

Discussion. Patients with obesity had higher levels of *Bacteroidetes*, *Proteobacteria* and lower levels of *Actinobacteria*, *Firmicutes*, TM7 (*Saccharibacteria*), *Fusobacteria*, and more frequently detected phyla *Tenericutes*, *Planctomycetes* and *Lentisphaerae* compared to healthy individuals. Metabolically healthy obese patients had more rarely detected phylum *Lentisphaerae* in their colonic microbiome, increased numbers of *Firmicutes* and reduced numbers of *Bacteroidetes* compared to metabolically unhealthy obese patients.

Conclusion. The findings demonstrate alterations in the colonic microbiome in patients with different obesity phenotypes.

Keywords: *metagenomic sequencing, colonic microbiome, obesity*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committees of the N.I. Pirogov Russian National Research Medical University and Rostov State Medical University.

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Научная статья
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Особенности микробиома толстой кишки у пациентов с ожирением при его различных фенотипах (оригинальная статья)

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Аннотация

Введение. На протяжении последних десятилетий разрабатывается концепция гетерогенности ожирения в зависимости от риска развития кардиометаболических осложнений, т.к. не все пациенты с ожирением склонны к развитию метаболической дисфункции.

Цель работы — изучить особенности микробных сообществ толстой кишки методом метагеномного анализа у пациентов с различными фенотипами ожирения и у здоровых людей.

Материалы и методы. Обследованы 265 человек (44 мужчины и 221 женщина, средний возраст 47,1 ± 4,8 года). Сформированы клинические группы: здоровые люди с нормальной массой тела (n = 129); пациенты с ожирением (n = 136), в том числе с метаболически здоровым (n = 40) и метаболически нездоровым (n = 55). Количественная и качественная оценка состояния микробиома кишечника выполнена путём метагеномного анализа. Из образцов кала выделяли ДНК и проводили секвенирование вариабельного участка v3-v4 гена *16S* рРНК.

Результаты. Выявлены статистически значимые (p < 0,05) различия количественных и качественных показателей изучаемых филотипов микроорганизмов толстой кишки у здоровых людей без ожирения и у пациентов с разными фенотипами ожирения.

Обсуждение. У пациентов с ожирением повышено количество *Bacteroidetes*, *Proteobacteria* и снижено содержание *Actinobacteria*, *Firmicutes*, TM7 (*Saccharibacteria*), *Fusobacteria*, а также чаще верифицируются филотипы *Tenericutes*, *Planctomycetes* и *Lentisphaerae* по сравнению с показателями у здоровых людей. У пациентов с метаболически здоровым ожирением в микробиоме толстой кишки реже регистрируется филотип *Lentisphaerae*, наблюдается повышение количества *Firmicutes* и снижение *Bacteroidetes* по сравнению с показателями при метаболически нездоровом ожирении.

Выводы. Полученные данные демонстрируют изменения микробиома толстой кишки у пациентов с разными фенотипами ожирения.

Ключевые слова: *метагеномное секвенирование, микробиом кишечника, ожирение*

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Background

The worldwide obesity prevalence has nearly tripled over the last 40 years. Obesity-related complications such as type 2 diabetes, dyslipidemia and arterial hypertension impair quality of life, reduce life expectancy and significantly increase health care costs [1]. However, some studies have found that obesity not always entails metabolic abnormalities and increased risk of cardiometabolic complications. In scientific literature, such phenotype of obesity is known as metabolically healthy obesity (MHO) [2]. Because of the lack of universally accepted criteria to identify MHO, its prevalence varies widely among studies — 3 to 57% of obese patients [1].

There are commonly known factors that can influence the etiology and pathogenesis of obesity, including eating habits, lifestyle, environment, genetic predisposition, etc. In the meantime, none of them can explain the rapidly increasing prevalence of obesity; therefore, researchers are gaining greater appreciation of other important contributory factors.

The role of the intestinal microbiome in the development of obesity has garnered a lot of attention from researchers [3]. Around 70% of microorganisms (MOs) inhabiting the human body reside in the colon where the bacterial cell density is estimated at 10^{11} to 10^{12} per 1 mL of the content. The number of microbial genes responsible for production of numerous gut metabolites exceeds 3 million. In the meantime, the human genome consists of approximately 23 thousand genes [4]. Therefore, in the context of the global obesity epidemic, it is of great interest to understand how exactly microbial metabolomes can alter the human metabolic profile [3]. In 2006, Turnbaugh et al. performed one of the first studies where they showed the relationship between the gut microbiota and weight gain [5]. Today, there have been offered different mechanisms, through which the intestinal microbiome can influence the metabolic homeostasis of a human. They include production of short-chain fatty acids, metabolic endotoxemia, fatty acid oxidation, involvement in lipogenesis, appetite regulation, etc. [6].

Although the gut microbiota had been studied for many years, one of the main challenges was associated with cultivation of a limited range of MOs. The innovative technology provided researchers with tools for phylogenetic identification and quantification of intestinal microbiome components through the analysis of nucleic acids. Most of these methods and techniques are based on extraction of DNA and amplification of the *16S* ribosomal RNA (rRNA) gene. It has been found that dominant phyla in the intestinal microbiome are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*, while the first 2 phyla represent 90% of the intestinal microbiome community [7]. There are data evidencing that increased levels of two phyla *Firmicutes* and *Actinobacteria* as well as decreased levels of *Bacteroidetes* and *Verrucomicrobia* are associated with obesity [8].

The aim of the study is to explore specific characteristics of colonic microbial communities in patients with different obesity phenotypes and in healthy individuals by using metagenomic analysis.

Materials and methods

The cohort cross-sectional study was conducted at Center for Molecular Health, which is a center for digital and translational biomedicine, Internal Medicine Department No. 3, the central research laboratory of the Rostov State Medical University and the Kazan (Volga Region) Federal University in 2018–2020. The research was approved by the local independent ethics committees of Pirogov National Research Medical University (minutes # 186 of 26/6/2019) and Rostov Medical University (minutes # 20/19 of 12/12/2019).

To minimize impacts of climatic conditions, dietary patterns and ethnic factors on the intestinal microbiome, the study enrollees included only those who lived in the same area (Rostov Region and Rostov-on-Don) during summer. A total of 265 individuals, including 44 (16.6%) men and 221 (83.4%) women; mean age 47.1± 4.8 years, were examined for the purpose of the further study.

Inclusion criteria:
- older than age 18 years;
- no antibiotics, prebiotics and probiotics taken 3 months before the study;
- signed informed consent for participation in the study.

Exclusion criteria:
- serious medical conditions (chronic kidney disease, chronic liver disease, chronic heart failure);
- any gastrointestinal diseases (including nonspecific ulcerative colitis, Crohn's disease, irritable bowel syndrome);
- any acute condition, depression, alcohol abuse, pregnancy.

The enrolled 265 individuals were further divided into two clinical groups: The 1st group was composed of subjects without obesity and metabolic disorders (the control group); the 2nd group included patients with obesity. Additional criteria were introduced for further stratification of the two groups.

Additional criteria for inclusion in the 1st group:
- body mass index (BMI) —18.5–24.9 kg/m^2;
- absence of metabolic disorders (dyslipidemia, hyperglycemia, hyperuricemia);
- absence of arterial hypertension.

Additional criteria for inclusion in the 2nd group:
- BMI ≥ 30 kg/m^2;
- waist circumference (WC) for men > 102 cm, for women > 88 cm.

Table 1. Clinical and laboratory profile of the participants

Indicator		Group 1 (*n* = 129)	Group 2 (*n* = 136)	*p*
Men	*n* (%)	15 (11,6)	28 (20,6)	0,6
Women	*n* (%)	114 (88,3)	108 (79,4)	0,6
Age, years	*M* ± *m*	39,6 ± 4,2	54,6 ± 4,7	0,03
BMI, kg/m^2	Me [min; max]	20,8 [19; 23]	34 [31; 36]	0,02
Waist, cm	Me [min; max]	74 [69; 75,5]	100 [95; 103]	0,01
Systolic blood pressure, mm Hg	Me [min; max]	120,5 [90; 125]	135 [125; 145]	0,03
Diasystolic blood pressure, mm Hg	Me [min; max]	74,5 [60; 90]	85 [80; 90]	0,001
Fasting plasma glucose, mmol/l	Me [min; max]	3,96 [4,05; 5,1]	5,57 [5,1; 6,93]	0,0001
Cholesterol, mmol/l	Me [min; max]	4,5 [4,1; 5,0]	5,42 [4,62; 6,2]	0,6
Low-density lipoprotein cholesterol, mmol/l	Me [min; max]	3,11 [2,4; 3,21]	3,19 [2,6; 3,64]	0,7
High-density lipoprotein cholesterol, mmol/l	Me [min; max]	1,93 [1,49; 2,24]	1,23 [1,11; 1,39]	0,03
Triglyceride, mmol/l	Me [min; max]	0,79 [0,57; 1,13]	1,65 [1,33; 2,34]	0,001

Table 2. The NCEP ATPIII criteria for assessment of the metabolic status of patients for the 2nd group

Criterion		Mean
Blood pressure, mm Hg	systolic	> 130
	diastolic	> 85
Triglyceride, mmol/l		≥ 1,7
High-density lipoprotein cholesterol, mmol/l	men	< 1,03
	female	< 1,29
Fasting plasma glucose, mmol/l		≥ 5,6
Waist, cm	men	102
	female	> 88
MHO criteria		<3 of the above indicators

Note. MHO — metabolic health obesity.

The 1st group was composed of 129 people: 15 (11.6%) men, 114 (88.3%) women; mean age 39.6 ± 4.2 years; mean BMI 20.8 ± 2.1 kg/m^2, WC 74 ± 5.8 cm.

The 2nd group included 136 patients with obesity: 28 (20.6%) men, 108 (79.4%) women; mean age 54.6 ± 4.7 years; mean BMI 33.8 ± 3.36 kg/m^2, WC 99.7 ± 7.3 cm.

The clinical and laboratory profile of the participants from the 1st and 2nd groups is given in **Table 1**.

To identify different obesity phenotypes by using NCEP-ATP III (The National Cholesterol Education Program, Adult Treatment Panel III)[1] criteria, patients from the 2nd group (**Table 2**) were divided into 2 subgroups:

- subgroup 2a — patients with MHO;
- subgroup 2b — patients with metabolically unhealthy obesity (MUO).

The healthy metabolic profile was set at fewer than 3 characteristics listed above [1]. Subgroups 2a and 2b were comparable in terms of age, BMI and WC.

Subgroup 2a was composed of 40 patients: 6 (15%) men, 34 (85%) women; mean age 49.5 ± 5.1 years; mean BMI 33.95 kg/m^2, WC 101.5 cm. Subgroup 2b included 55 patients: 11 (20%) men, 44 (80%) women; mean age 51.3± 3.6 years; mean BMI 33.6 kg/m^2; WC 98.9 cm. The clinical and laboratory profile of patients from subgroups 2a and 2b is given in **Table 3**.

All the participants were asked to submit their current complaints and past medical records; all of them

[1] NCEP ATPIII — The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), USA

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Table 3. Clinical and laboratory characteristics of patients 2a and 2b subgroups (*M* ± *m*)

Indicator	Subgroup 2a (*n* = 40)	Subgroup 2b (*n* = 55)	*p*
Men	6 (15%)	11 (20%)	0,6
Women	34 (85%)	44 (80%)	0,6
Age	49,05 ± 5,1	51,3 ± 3,6	0,7
Body mass index, kg/m^2	34 ± 3,98	33,6 ± 3,39	0,8
Waist, cm	102 ± 8,37	98,9 ± 7,63	0,1
Systolic blood pressure, mm Hg	116 ± 11,5	143 ± 10,1	**<0,0001**
Diasystolic blood pressure, mm Hg	74,4 ± 7,53	90,2 ± 7,7	**<0,0001**
Fasting plasma glucose, mmol/l	4,87 ± 0,5	7,72 ± 2,36	**<0,0001**
Immunoreactive insulin, pg/ml	470 ± 565	550 ± 439	0,1
Index of insulin resistance	10,3 ± 12,3	20,4 ± 20,5	**0,0003**
Cholesterol, mmol/l	5,28 ± 1,16	5,67 ± 1,37	0,1
Low-density lipoprotein cholesterol, mmol/l	3,28 ± 0,91	3,05 ± 1,33	0,3
High-density lipoprotein cholesterol, mmol/l	1,38 ± 0,29	1,27 ± 0,29	0,04
Triglyceride, mmol/l	1,25 ± 0,54	2,58 ± 1,14	<0,0001

were examined through general checkups and had their body measurements taken (weight, height, WC, BMI). The relationship between the dietary intake and the obesity metabolic status was assessed by using food frequency questionnaires and food records. BMI was calculated following WHO experts' guidelines (2003). WC was measured using a measuring tape midpoint between the lower margin of the last palpable rib and the iliac crest. Blood pressure was measured using a manual monitor and standard Korotkoff method.

For the purpose of carbohydrate metabolism evaluation, all the participants had their fasting blood sugar and immunoreactive insulin levels checked; the insulin resistance index was calculated by the formula: fasting blood glucose (mmol/L) × fasting insulin (u/L)/22.5. The lipid metabolism was assessed by measuring total cholesterol, low and high density lipoprotein cholesterol, and serum triglycerides. Insulin levels were measured by a Magpix analyzer (BioRad) and the Milliplex: Human Adipokine Magnetic Bead Panel 2 kit.

The Hitachi U-2900 spectrophotometer and Olvex Diagnosticum reagent kits were used for biochemical assays. Fecal samples were collected following the guidelines [9]. The metagenomic analysis of the intestinal community was performed at the Interdisciplinary Center of Shared Facilities of the Kazan Federal University. The QIAamp DNA stool mini kit (Qiagen) was used to extract DNA from stool samples. The variable v3-v4 region of the *16S* rRNA gene was sequenced using the Illumina MiSeq platform. Sequences of *16S* rRNA genes were analyzed using the QIIME v.1.9.1 software and the Greengenes v.13.8 reference OTUs pre-clustered at the 97% sequence identity threshold. The relative abundance of bacterial taxa in the total reads is shown as a percentage range (0-1) based on the number of mapped reads for each taxon. Shannon, Simpson, and Chao1 and phylogenetic diversity indices were used to measure the alpha-diversity of the bacterial community.

The R version RStudio v.3.2 software was used for statistical analysis. The variables were checked for normal distribution using the Shapiro-Wilk test. Mean squared deviations, the median and quartiles (25%, 75%), minimum and maximum values in the sample were used as descriptive statistics for quantitative variables. The means in the groups were compared using the Mann-Whitney test; frequencies (%) were compared with the help of Fisher's exact test. The latter test was used together with the Holm correction for multiple comparisons for detection frequencies of phylotypes detected in the colon. The median abundancies of the studied phylotypes and MOs detected in the colon were compared using the Kruskal-Wallis test (pairwise comparisons based on the post-hoc Nemenyi test). Differences were recognized as statistically significant at $p < 0.05$.

Results

Six dominant MO phylotypes were detected in the intestinal microbiome of participants from the 1st and 2nd groups, namely: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrobia* and the phylum

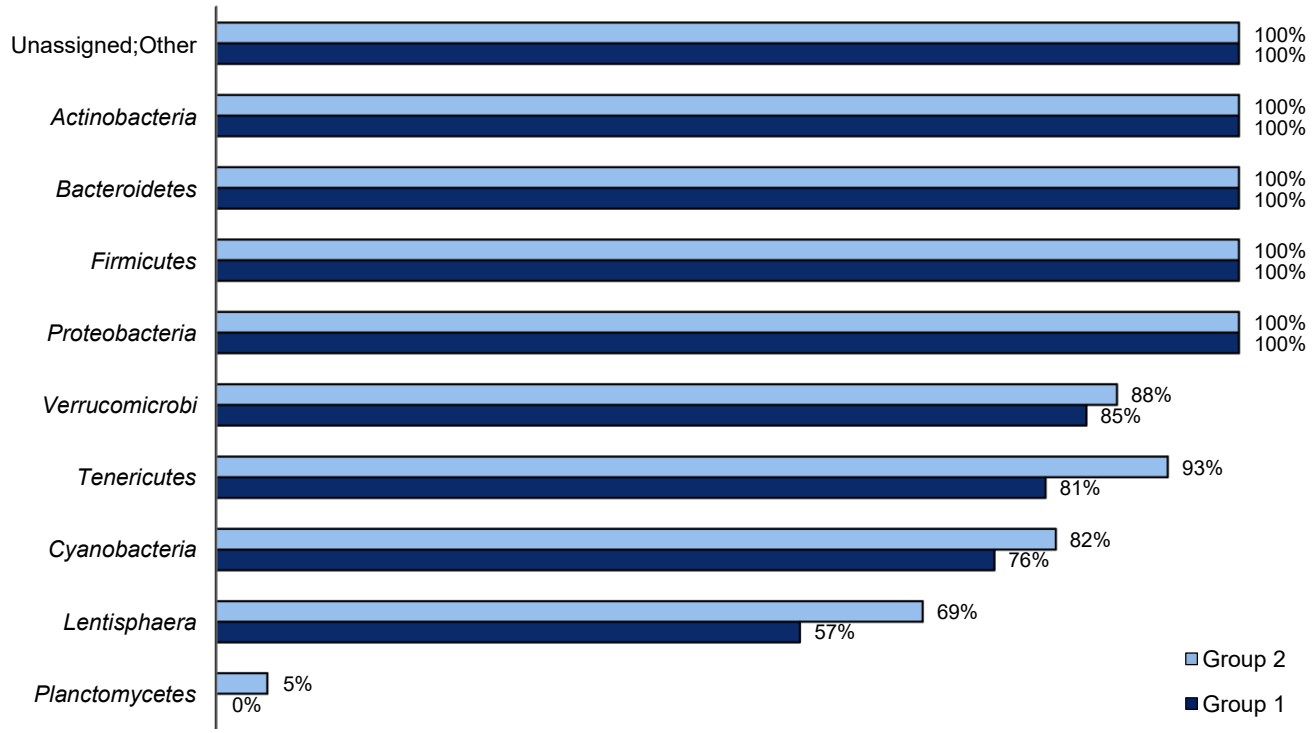
Unassigned (Other). The unassigned group was represented by sequences having no matches in the reference database; therefore, these can be unknown bacteria or sequencing artifacts. In addition to the above phyla, the control group and the group of obese patients showed the dominance of *Tenericutes* (81 and 93% respectively) and *Cyanobacteria* (76 and 82% respectively) by frequency of detection. Significant differences were identified for 3 phyla: *Tenericutes* ($p = 0.007$), *Planctomycetes* ($p = 0.03$), *Lentisphaerae* ($p = 0.047$) (**Figure**).

The comparative analysis of the quantitative variables of the 1st and 2nd groups helped identify significant ($p < 0.05$), though bidirectional differences for 7 phyla (*Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Cyanobacteria*, TM 7 (*Saccharibacteria*), *Fusobacteria*) (**Table 4**). For example, in the group of obese patients, 3 phyla (*Bacteroidetes*, *Proteobacteria*, *Cyanobacteria*) demonstrated an increase ($p < 0.05$) in their levels, while 4 phyla (*Actinobacteria*, *Firmicutes*, TM 7 (*Saccharibacteria*), *Fusobacteria*) showed decreased levels.

The phylogenetic diversity indices as well as Shannon, Simpson, and Chao1 were calculated for assessment of the alpha-diversity (**Table 5**). Significant differences between the control group and the group of obese patients were identified for the phylogenetic diversity index and the Chao1 index, thus suggesting a reduction in the alpha-diversity in fecal samples from the obese patients. On the other hand, the Shannon index did not demonstrate any difference in the groups

Table 4. Significant differences in quantitative variables for some MO phylotypes in the participants' colon, Me [min; max]

Phylotypes	Group 1 ($n = 129$)	Group 2 ($n = 136$)	*p*
Bacteroidetes	0,3 [0,2; 0,43]	0,38 [0,3; 0,47]	0,0001
Proteobacteria	0,014 [0,0087; 0,028]	0,025 [0,013; 0,052]	<0,0001
Cyanobacteria	0,00027 [0,00014; 0,0014]	0,00059 [0,00021; 0,002]	0,02
Actinobacteria	0,023 [0,012; 0,055]	0,0098 [0,0054; 0,021]	<0,0001
Firmicutes	0,59 [0,48; 0,68]	0,52 [0,43; 0,59]	<0,0001
TM7 *(Saccharibacteria)*	0,000069 [0,000069; 0,00014]	0,00013 [0,00007; 0,00021]	0,04
Fusobacteria	0,000074 [0,000069; 0,00021]	0,00028 [0,000074; 0,0012]	0,007



The frequency of detection of some MO phylotypes in feces of the participants.

*$p < 0.05$ as compared with the 1st group.

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Table 5. Indices of the MO phylogenetic diversity in the 1st and 2nd groups (*M* ± *SD*)

Index	Group 1 (*n* = 129)	Group 2 (*n* = 136)	*p*
Phylogenetic diversity index	42,92 ± 7,45	40,30 ± 7,41	0,00111
Chao1 index	4114,3 ± 1282,0	3771,2 ± 1539,1	0,00705
Shannon index	7,73 ± 0,81	7,60 ± 0,94	0,09153
Simpson index	0,97 ± 0,02	0,97 ± 0,02	0,2184
Number of operational taxonomic units	1993,1 ± 549,67	1895,7 ± 706,28	0,06655

and was significantly higher compared to the previously published data for the comparable group of patients with carbohydrate metabolism disorders [10]. However, these values of the Shannon index are not extreme and can be found in research literature with reference to stool samples from healthy individuals [11, 12].

When analyzing the detection frequencies for the studied MO phylotypes in patients with MHO and MUO, significant differences were found only for the phylum *Lentisphaerae*, which was more rarely (p = 0.03) detected in subgroup 2b. The analysis of quantitative variable revealed significant (p = 0.03) differences, namely increased *Bacteroidetes* and decreased *Firmicutes* levels in subgroup 2b.

The detection frequencies for the studied MO phylotypes in subgroups 2a and 2b were compared with the frequencies demonstrated by the healthy individuals (the 1st group) (**Table 6**). The general tendency was identified, showing 100% presence of 5 phyla (Unassigned (Other), *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*) and absence of 4 phyla (*Planctomycetes*, WPS-2 (*Eremiobacterota*), *Gemmatimonadetes* and *Acidobacteria*) in the intestinal microbiome. The phyla *Verrucomicrobia*, *Tenericutes*, and *Cyanobacteria* were dominant in the 1st group, subgroups 2a and 2b in terms of detection frequency. In subgroup 2a, *Tenericutes* and *Lentisphaerae* were detected significantly more frequently (p = 0.002 and p = 0.0009 respectively) than in subgroup 2b and the 1st group.

General tendencies were also revealed by the analysis of quantitative variables in the studied groups. The quantitative levels of the phylum Unassigned (Other) were significantly increased, while the *Actinobacteria* levels were decreased in subgroups 2a and 2b compared to the 1st group. However, statistically significant differences in 4 other phyla were found only in subgroup 2b. For example, quantitative variables for *Bacteroidetes*, *Proteobacteria,* and *Fusobacteria* were significantly higher ($p < 0.05$) and for *Firmicutes* – lower than the comparable variables in subgroup 2a and the 1st group (**Table 7**).

Discussion

The analysis of the questionnaires and food records did not show any significant difference in the total consumption of energy and macronutrients in individuals with two obesity phenotypes, thus being consistent with the results of most of the other related studies [13]. However, literature data about the role of nutrition in development of the MHO phenotype are controversial [14]. The currently available clinical and experimental data suggest that changes in the colonic microbiome can be a potential pathogenetic factor for development of obesity and metabolic syndrome.

Studies employing animal models and obese individuals confirmed specific changes in the composition of the intestinal microbiome, though the obtained results are controversial. For example, some researchers detected decreasing numbers of *Bacteroidetes* and increasing numbers of *Firmicutes* in obesity [15, 16]. Schwiertz et al., on the contrary, reported a significant increase in the number of *Bacteroidetes* in obese and overweight individuals [17]. Duncan et al. did not find any correlation between BMI and changes in the *Firmicutes* and *Bacteroidetes* ratio [18].

During our study, we found quantitative and qualitative changes in the intestinal microbiome in obese individuals compared to healthy individuals and between the patients with different obesity phenotypes. The comparative analysis of quantitative variables of the studied colonic MO phylotypes in healthy individuals and obese patients revealed bidirectional statistically significant differences for 7 phyla: The increase in the studied variables for *Bacteroidetes*, *Proteobacteria*, *Cyanobacteria* and the decrease for *Actinobacteria*, *Firmicutes*, TM7 (*Saccharibacteria*), *Fusobacteria*. Despite the significant differences in quantitative variables for the above phylotypes, no statistically significant differences in frequencies of their detection were found in the 1st and 2nd groups. At the same time, *Tenericutes*, *Planctomycetes* and *Lentisphaerae* were significantly more frequently ($p < 0.05$) detected in the group of obese patients.

The data of our study show that the frequency of detection of the phylum *Cyanobacteria* in the control

Table 6. Comparison of detection frequencies for MO phylotypes in the participants of the 1st group, subgroups 2a and 2b, abs. (%)

Phylotypes	Group 1	Subgroup 2a	p_{1-2a}	Subgroup 2b	p_{1-2b}
Unassigned;Other	129 (100)	40 (100)	–	55 (100)	–
Actinobacteria	129 (100)	40 (100)	–	55 (100)	–
Bacteroidetes	129 (100)	40 (100)	–	55 (100)	–
Firmicutes	129 (100)	40 (100)	–	55 (100)	–
Proteobacteria	129 (100)	40 (100)	–	55 (100)	–
Verrucomicrobia	110 (85)	35 (88)	1	47 (85)	1
Tenericutes	104 (81)	40 (100)	002	50 (91)	0,1
Cyanobacteria	98 (76)	34 (85)	0,8	45 (82)	0,9
Lentisphaerae	73 (57)	35 (88)	0009	36 (65)	0,3
Euryarchaeota	55 (43)	20 (50)	0,9	20 (36)	0,9
Elusimicrobia	37 (29)	17 (42)	0,24	11 (20)	0,27
TM7 (*Saccharibacteria*)	37 (29)	9 (22)	0,54	7 (13)	0,07
Synergistetes	31 (24)	6 (15)	0,6	16 (29)	0,6
Fusobacteria	25 (19)	9 (22)	1	14 (25)	1
Bacteria;Other	8 (6)	3 (8)	1	6 (11)	1
Crenarchaeota	5 (4)	4 (10)	0,44	0	0,44
Chloroflexi	1 (1)	0	1	0	1
Parvarchaeota	1 (1)	0	1	0	1
WS3 (*Latescibacteria*)	1 (1)	0	1	0	1
Spirochaetes	0	1 (2)	0,7	1 (2)	0,7
Acidobacteria	0	0	–	1 (2)	0,6
Planctomycetes	0	0	–	0	–
WPS-2 (*Eremiobacterota*)	0	0	–	0	–
Gemmatimonadetes	0	0	–	0	–

Note. Pairwise comparisons were performed by using Fisher's exact test and the Holm correction for multiple comparisons; "–" – no variations for calculation of *p*.

group and in the group of obese patients was 76 and 82%, respectively. In the meantime, the literature data confirm that the phylum *Cyanobacteria* is present in insignificant amounts in human fecal samples. Most likely that during the study, chloroplasts of plants had been sequenced from the consumed food, as the study was performed during summer when vegetable food accounted for the largest percentage in the dietary intake [19].

To date, very few studies have addressed the role of the intestinal microbiome in MHO development. One of the experimental studies found that the intestinal microbiome in mice with obesity and type 2 diabetes, as compared to mice with MHO, was characterized by a 20% decrease in *Firmicutes* to the benefit of *Bacteroidetes* and stable frequency of occurrence of the phylum *Actinobacteria* [20]. In our study, the occurrence frequency for the studied MO phylotypes in the patients with MHO and MUO was different only for the phylum *Lentisphaerae*, the occurrence of which was statistically higher in patients with MHO. However, the analysis of quantitative variables of 24 studied phylotypes in the subgroups of patients with MHO and MUO demonstrated statistically significant differences ($p = 0.03$) for two of them, namely for *Bacteroidetes* and for *Firmicutes*, the levels of which were increased and decreased, respectively, in the subgroup of patients with MUO.

Thus, the colonic microbiome in healthy individuals demonstrates certain differences from the colonic

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Table 7. Significant differences in intestinal microbiome quantitative variables among the participants, Me [min; max]

Phylotypes	Group 1	Subgroup 2a	p_{1-2a}	Subgroup 2b	p_{1-2b}
Unassigned;Other	0,021 [0,014; 0,028]	0,038 [0,019; 0,047]	<0,0001	0,028 [0,017; 0,041]	0,03
Actinobacteria	0,023 [0,012; 0,055]	0,013 [0,0076; 0,027]	0,009	0,011 [0,0061; 0,021]	<0,0001
Bacteroidetes	0,3 [0,2; 0,43]	0,35 [0,26; 0,42]	0,6	0,43 [0,34; 0,5]	<0,0001
Firmicutes	0,59 [0,48; 0,68]	0.56 [0.48; 0.59]	0,2	0,46 [0,38; 0,54]	<0,0001
Proteobacteria	0,014 [0,0087; 0,028]	0.019 [0.0092; 0.043	0,31	0,027 [0,021; 0,055]	<0,0001
Fusobacteria	0,000074 [0,000069; 0,00021]	0,00015 [0,000072; 0,00021]	0,7	0,00055 [0,00014; 0,0018]	0,01

microbiome in obesity and its different phenotypes. However, identification of microbial biomarkers for obesity and its phenotypes needs further studies, which would address not only MO phylotypes detected in the colon, but also generic and specific characteristics of their representatives.

Conclusions

1. 5 MO phylotypes (Unassigned/Other, *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*) were detected in 100% of healthy adult individuals and obese patients in their intestinal microbiome (based on the example of residents from Rostov-on-Don and Rostov Region); the phylum *Verrucomicrobia* was detected in 85 and 88% of the participants, respectively; the phylum *Tenericutes* was detected in 81 and 93%, respectively.

2. In the obese patients, the intestinal microbiome demonstrates significantly ($p < 0.05$) increased frequencies of detection of *Tenericutes*, *Planctomycetes* and *Lentisphaerae* as compared to the similar detection frequencies in the healthy participants.

3. In the obese patients, the intestinal microbiome demonstrates a statistically significant ($p < 0.05$) increase in the levels of *Bacteroidetes*, *Proteobacteria* and a decrease in the levels of *Actinobacteria*, *Firmicutes*, TM 7 (*Saccharibacteria*), *Fusobacteria* as compared to the levels of these phyla in the healthy participants.

4. The phylum *Lentisphaerae* is detected significantly more rarely ($p= 0.03$) in the intestinal microbiome of the patients with the MHO phenotype as compared with the patients with MUO.

5. The patients with the MUO phenotype demonstrate significantly ($p < 0.05$) higher levels of *Bacteroidetes* and lower levels of *Firmicutes* compared to the patients with MHO.

6. The comparative analysis of the detection frequencies for the studied phylotypes in patients with different obesity phenotypes and in healthy people demonstrated significant differences in levels of two phyla: *Tenericutes* ($p = 0.002$) and *Lentisphaerae* ($p = 0.0009$) only in the MHO patients, but not in the MUO patients.

7. In the MUO patients, the intestinal microbiome is characterized by significantly ($p < 0.05$) higher levels of *Bacteroidetes*, *Proteobacteria*, *Fusobacteria* and lower levels of *Firmicutes* as compared to the microbiome in the healthy individuals.

8. In the MHO patients, the intestinal microbiome is characterized by significantly ($p < 0.05$) higher levels of the unidentified phylum (Unassigned/Other) and lower levels ($p < 0.05$) — of *Actinobacteria* as compared to the microbiome in the healthy individuals.

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