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Features of bacterial DNA taxonomy in blood of patients with various metabolic phenotypes of obesity

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ABSTRACT

Aim. To study the blood microbiome taxonomy in patients with metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUHO).

Materials and methods. The study included healthy donors without obesity (n = 116) and obese patients who were divided into subgroups with MHO (n = 36) and MUHO (n = 53). Bacterial DNA isolated from blood samples was subject to metagenomic sequencing of the v3–v4 variable region in the 16S rRNA gene. We compared the frequency of isolating certain taxa from the samples and the proportion of these taxa in the total pool of bacterial DNA in the blood.

Results. MUHO patients showed an increase in Lachnospiraceae, Ruminococcaceae, and Prevotellaceae, which are the main taxa in gut microbiota. This may indicate greater intestinal permeability in such patients. Obese patients, regardless of the metabolic phenotype of obesity, more often had Rhodobacteraceae, Streptomycetaceae, Leuconostocaceae, and Burkholderiaceae DNA in their blood. Nocardioidaceae, Flavobacteriaceae, Hyphomicrobiaceae, and Gaiellaceae DNA were more frequently present in the blood microbiome of patients with MHO, whereas MUHO patients more often had S24-7, Nocardiaceae, and Helicobacteraceae DNA in their blood. Many members of these families inhabit soil and water, which may indicate increased skin barrier permeability in obese patients. Additionally, a higher number of Helicobacteraceae-positive blood samples in the MUHO patient group may indicate increased translocation from the stomach.

Conclusion. Obesity is accompanied by changes in the taxonomic composition of the blood microbiome. Moreover, the nature of the changes depends on the metabolic phenotype of obesity and the permeability of external barriers.

Keywords: blood microbiome, bacterial DNA in blood, obesity, metabolically healthy obesity, metabolically unhealthy obesity

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Pirogov Russian National Research Medical University (Protocol No.186 of 26.06.2019) and Rostov State Medical University (Protocol No. 20/19 of 12.12.2019).

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Особенности таксономической принадлежности бактериальной ДНК крови у пациентов с различными метаболическими фенотипами ожирения

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РЕЗЮМЕ

Цель. Изучить таксономический состав микробиома крови у пациентов со следующими фенотипами: метаболически здоровым ожирением (МЗО) и метаболически нездоровым ожирением (МНЗО).

Материалы и методы. В исследование включены здоровые доноры без ожирения (n = 116) и пациенты с ожирением, которые были разделены на подгруппы с МЗО (n = 36) и МНЗО (n = 53). Из образцов венозной крови выделяли бактериальную ДНК и проводили метагеномное секвенирование вариабельного участка v3–v4 гена 16S рРНК. Сравнивалась как частота выделения отдельных таксонов из образцов, так и доля, приходящаяся на эти таксоны в общем пуле бактериальной ДНК крови.

Результаты. Для пациентов с МНЗО было характерно увеличение доли Lachnospiraceae, Ruminococcaceae

и Prevotellaceae, которые являются основными представителями кишечной микробиоты, что может являться следствием большей кишечной проницаемости, характерной для таких пациентов. Вне зависимости от метаболического фенотипа у пациентов с ожирением из образцов крови чаще выделялась ДНК Rhodobacteraceae, Streptomycetaceae, Leuconostocaceae и Burkholderiaceae. При МЗО также чаще обнаруживалась в крови ДНК Nocardioidaceae, Flavobacteriaceae, Hyphomicrobiaceae и Gaiellaceae, а у пациентов с МНЗО – S24-7, Nocardiaceae и Helicobacteraceae. Многие представители этих семейств являются обитателями почв и вод, что может свидетельствовать об усилении проницаемости кожного барьера у пациентов с ожирением. Также большая представленность Helicobacteraceae у пациентов с МНЗО может указывать на усиление транслокации из желудка.

Заключение. Ожирение приводит к выраженным изменениям в таксономическом составе микробиома крови, при этом характер изменений зависит от метаболического фенотипа ожирения и проницаемости внешних барьеров.

Ключевые слова: микробиом крови, бактериальная ДНК крови, ожирение, метаболически здоровое ожирение, метаболически нездоровое ожирение

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

Источник финансирования. Работа выполнена в рамках договора № 0373100122119000041 по проекту «Создание банка биообразцов сыворотки крови и фекалий от здоровых доноров и пациентов с ожирением, метаболическим синдромом, сахарным диабетом II типа, нарушением мукозального барьера желудочно-кишечного тракта с целью выявления кандидатных видонеспецифических медиаторов систем quorum sensing микробиоты человека, модулирующих эндокринную и метаболическую функцию жировой ткани».

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом РНИМУ им. Н.И. Пирогова (протокол № 186 от 26.06.2019) и РостГМУ (протокол № 20/19 от 12.12.2019).

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INTRODUCTION

Since the beginning of the XX century and the development of DNA sequencing technologies, works have appeared demonstrating the presence of bacterial DNA encoding 16S rRNA in blood samples obtained from both healthy individuals and patients with various pathologies [1–3]. To date, evidence of the presence of human blood microbiome is undoubtful, but its role in pathology remains unclear. The main source of microbial DNA in the blood is bacterial translocation from the gut and, to a lesser extent, from extraintestinal microbiomes [3].

There is a decrease in the diversity of gut microbiota in obesity compared to healthy donors, and body mass index (BMI) is negatively correlated with the total amount of microbial DNA in the gut [4, 5]. At the same time, an increase in blood microbiome diversity is observed in obese individuals [6]. Metabolic disorders are associated with increased intestinal permeability due to both internal (e.g., hyperglycemia) and external (changes in the gut microbiome, presence of excessive carbohydrates and / or fats in the diet) causes [7]. Obesity, however, does not always lead to the development of metabolic disorders, so there are metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUHO) phenotypes, respectively [8]. To date, there are no works demonstrating differences in the taxonomic composition of the blood microbiome depending on the metabolic phenotype of obesity, which became the aim of our study.

MATERIALS AND METHODS

A one-stage cohort study was carried out from 2018 to 2020 at the Center for Digital and Translational Biomedicine LLC, Center for Molecular Health, Department of Internal Medicine No. 3, RostSMU, Ministry of Health of Russia and Kazan (Volga Region) Federal University. Two groups were included in the study: a control group and obese patients. The con-

trol group included 116 healthy donors (BMI 18.5–24.9 kg / m^2) without metabolic disorders and arterial hypertension. The selection criteria for the obese patient group were BMI ≥ 30 kg / m^2 and waist circumference greater than 102 cm in men or 88 cm in women. According to the NCEP-ATP III criteria, obese patients were divided by the metabolic phenotype into a group with MHO (n = 36) and with MUHO (n = 53). Obesity was considered metabolically unhealthy if the patient was characterized by three or more criteria: 1) waist circumference (> 102 cm in men; > 88 cm in women); 2) serum triglycerides (≥ 1. 7 mmol / l); 3) high-density lipoprotein (HDL) cholesterol (< 1.03 mmol / l in men; < 1.29 mmol / l in women); 4) blood pressure (systolic ≥ 130 mm Hg; diastolic ≥ 85 mm Hg); 5) fasting glucose (≥ 5.6 mmol / l) [9].

Venous blood sampling followed by microbial DNA isolation was performed in all individuals according to the manufacturer's protocol (QIAamp BiOstic Bacterimia DNA Kit, Qiagen, Germany). Sequencing of the v3–v4 variable region of the 16S rRNA gene was performed on the Illumina MiSeq platform (USA) according to the manufacturer's recommendations. The obtained 16S rRNA gene sequences (reads) were analyzed using QIIME software (version 1.9.1) and Greengenes reference database (v. 13.8) with 97% similarity threshold between sequences. Data on taxon representation in the total pool of reads are given in fractions (0–1), which were calculated based on the number of mapped reads for each taxon. In addition, the frequency of DNA detection from the blood samples in each of the studied groups (%) was analyzed.

A statistical analysis was performed using the MedCalc® Statistical Software platform (MedCalc Software Ltd, Belgium). Given the absence of normal distribution in the fractions of individual taxa in the total pool of bacterial DNA in the blood, the data are presented as the median and the interquartile range Me [Q_{25}–Q_{75}]. A comparative analysis of the data sets was performed using the Kruskal – Wallis test. To establish the differences in the frequency of taxa in patients of different groups, the Pearson's chi-square test was used. The differences were considered statistically significant at $p \leq 0.05$.

RESULTS

We analyzed the taxonomic composition of the blood microbiome at the level of families that were identified in more than 25% of patients in at least one of the studied groups. On the one hand, the choice of families as a studied taxonomic level was explained by the fact that it provided a sufficiently detailed description of the blood microbiome and, on the other hand, included a relatively small number of unidentified taxa. The data obtained were compared by the frequency of detection of families from the blood samples (%) and by the proportion of each taxon in the total pool of bacterial DNA in the blood.

Lachnospiraceae, Ruminococcaceae, Prevotellaceae, Bacteroidaceae, Sphingomonadaceae, Staphylococcaceae, Corynebacteriaceae, Moraxellaceae, Micrococcaceae, Propionibacteriaceae were the main families in the blood microbiome. DNA from each of these families was detected in more than 75% of patients and accounted for more than 0.02% of the total bacterial DNA pool in the blood. In total, these families accounted for 0.548 [0.417–0.619] of the microbial DNA in the blood.

Both MHO and MUHO patients were characterized by specific changes in the blood microbiome, which was manifested both by changes in the proportion of individual families in the total bacterial DNA pool and in the frequency of detection of individual taxa (Table 1).

Table 1

Identified differences in the DNA content of individual families in the blood in MHO and MUHO patients, %, Me [Q_{25}–Q_{75}]

Family	Control group	Patients with MHO	Patients with MUHO
Lachnospiraceae	97.41% 0.103 [0.044–0.160]	97.22% 0.092 [0.033–0.211]	98.11% 0.152 [0.092–0.207]*
Ruminococcaceae	96.55% 0.083 [0.033–0.152]	100.00% 0.070 [0.038–0.114]	98.11% 0.117 [0.059–0.139]†
Prevotellaceae	86.21% 0.029 [0.012 – 0.065]	94.44% 0.036 [0.011–0.103]	94.34% 0.049 [0.025–0.115]*
Staphylococcaceae	93.97% 0.023 [0.009–0.053]	97.22% 0.018 [0.007–0.047]	88.68% 0.009 [0.004–0.027]*†
Caulobacteraceae	70.69% 0.010 [0.000–0.029]	58.33% 0.004 [0.000–0.024]	62.26% 0.003 [0.000–0.012]*
Rhodobacteraceae	39.66% 0.000 [0.000–0.008]	55.56%* 0.002 [0.000–0.012]	64.15%* 0.005 [0.000–0.011]*
Sphingomonadaceae	75.86% 0.022 [0.002–0.052]	75.00% 0.009 [0.000–0.060]	75.47% 0.005 [0.001–0.015]*†
S24-7	31.90% 0.000 [0.000–0.002]	47.22% 0.000 [0.000–0.007]*	69.81%* 0.005 [0.000–0.018]*†
Nocardiaceae	35.34% 0.000 [0.000–0.006]	50.00% 0.001 [0.000–0.010]	52.83%* 0.001 [0.000–0.010]
Nocardioidaceae	31.03% 0.000 [0.000–0.003]	50.00%* 0.000 [0.000–0.007]	41.55% 0.000 [0.000–0.007]
Streptomycetaceae	15.52% 0.000 [0.000–0.000]	33.33%* 0.000 [0.000–0.005]*	33.96%* 0.000 [0.000–0.003]*

Table (continued)

Family	Control group	Patients with MHO	Patients with MUHO
Flavobacteriaceae	25.00% 0.000 [0.000–0.000]	52.78%* 0.001 [0.000–0.014]*	26.42%† 0.000 [0.000–0.001]†
Helicobacteraceae	12.93% 0.000 [0.000–0.000]	16.67% 0.000 [0.000–0.000]	26.42%* 0.000 [0.000–0.001]
Burkholderiaceae	35.34% 0.000 [0.000–0.004]	55.56%* 0.001 [0.000–0.006]	54.72%* 0.001 [0.000–0.007]
Hyphomicrobiaceae	16.38% 0.000 [0.000–0.000]	41.67%* 0.000 [0.000–0.005]*	24.53% 0.000 [0.000–0.000]†
Bradyrhizobiaceae	44.83% 0.000 [0.000–0.008]	33.33% 0.000 [0.000–0.005]	22.64%* 0.000 [0.000–0.000]*
[*Barnesiellaceae*]	38.79% 0.000 [0.000–0.011]	11.11%* 0.000 [0.000–0.000]*	35.81%† 0.000 [0.000–0.009]†
Leuconostocaceae	9.48% 0.000 [0.000–0.000]	27.78%* 0.000 [0.000–0.001]*	32.08%* 0.000 [0.000–0.002]*
Gaiellaceae	15.52% 0.000 [0.000–0.000]	30.56%* 0.000 [0.000–0.002]	20.75% 0.000 [0.000–0.000]
Verrucomicrobiaceae	33.62% 0.000 [0.000–0.005]	16.67%* 0.000 [0.000–0.000]*	47.17%† 0.000 [0.000–0.012]†

* differences are significant compared to the control group ($p \leq 0.05$), † differences are significant compared to patients with MHO ($p \leq 0.05$).

Most of the changes in the blood microbiome in patients with MHO and MUHO were characterized by increasing frequency of DNA detection of individual families in the blood samples, which in some cases entailed an increase in the proportion of these taxa in the total pool of bacterial DNA in the blood. Regardless of the metabolic phenotype, DNA from the *Rhodobacteraceae, Streptomycetaceae, Leuconostocaceae,* and *Burkholderiaceae* families was more frequently detected in obese patients. *Nocardioidaceae, Flavobacteriaceae, Hyphomicrobiaceae*, and *Gaiellaceae* DNA was also detected in the blood of individuals with MHO, and *S24-7*, *Nocardiaceae*, and *Helicobacteraceae* DNA was detected in patients with MUHO. At the same time, in MUHO patients, *Lachnospiraceae* and *Prevotellaceae* were more abundant compared to Group 1 and *Ruminococcaceae* were more abundant compared to MHO patients, despite similar frequency of isolation of these families from the blood samples of each study group. These taxa accounted for about ⅕ of the total pool of bacterial DNA in the blood in healthy donors and patients with MHO, whereas in MHO patients, these families accounted for almost ⅓.

In addition, in both MHO and MUHO patients, there was a decrease in the proportion of several families in the blood microbiome. DNA [*Barnesiellaceae*] and *Verrucomicrobiaceae* were less frequently isolated from the blood in patients with MHO. In MUHO patients, the content of *Staphylococcaceae*, *Caulobacteraceae*, and *Sphingomonadaceae* was lower compared to Group 1, despite similar frequency of detecting DNA of these taxa from the blood samples. Moreover, *Bradyrhizobiaceae* DNA was detected less frequently in these patients.

DISCUSSION

The obtained data indicate that obesity leads to significant changes in the blood microbiome at the family level, and the features of the blood microbiome depend on the metabolic phenotype of obesity. At the phylum level, the taxonomic composition of the blood microbiome is similar in healthy donors and obese patients [6].

Both the patients with MHO and patients with MUHO were characterized by the spectrum of taxa whose DNA was detected from the blood samples of these patients more frequently than in the control group. Interestingly, representatives of *Rhodobacteraceae, Streptomycetaceae, Burkholderiaceae, Nocardioidaceae, Flavobacteriaceae, Hyphomicrobiaceae, Gaiellaceae*, and *Nocardiaceae*, which were detected in the blood samples of MHO and MUHO patients with increased frequency, are mostly soil and water inhabitants. Such habitats suggest that translocation of DNA from these taxa into the blood may occur from the surface of the skin or respiratory tract. Obese patients are characterized by a large body surface area, which may cause increased percutaneous translocation of microbial DNA. In addition, obesity causes changes in skin physiology and leads to increased permeability of the skin barrier [10]. It seems that obesity, regardless of its metabolic phenotype, is accompanied by increased translocation of bacterial DNA from the skin surface.

An increase in the proportion of the *Lachnospiraceae, Ruminococcaceae,* and *Prevotellaceae* families in the total pool of bacterial DNA in the blood was noted in patients with MUHO. Representatives of these families are anaerobes and the main representatives of the gut microbial flora. MUHO is associated with the presence of smoldering systemic inflammation and greater permeability of the intestinal wall [7, 8]. Thus, it can be assumed that the increased proportion of *Lachnospiraceae, Ruminococcaceae,* and *Prevotellaceae* in MUHO is a consequence of greater translocation of microbial DNA from the intestine, common in such patients.

An increased frequency of *Helicobacteraceae* DNA detection was also prevailing in MUHO pa-

tients. Since the main representative of this family is *Helicobacter pylori*, it can be assumed that MUHO is also associated with increased permeability of the gastric wall to bacterial DNA. Thus, MUHO seems to be characterized by increased microbial translocation from both intestinal and extraintestinal microbiomes, which can be caused by damaged barrier in the presence of chronic inflammation.

CONCLUSION

Obesity, regardless of its metabolic phenotype, is accompanied by changes in the taxonomic composition of bacterial DNA in the blood. Both MHO and MUHO are characterized by an increase in the frequency of isolating DNA of soil and water resident families, which may indicate large translocation of microbial DNA from the skin surface. At the same time, patients with MUHO also have an increased content of DNA of gastric and intestinal flora representatives in the blood, which may indicate greater permeability of these barriers to bacterial DNA. Thus, changes in the taxonomic composition of the blood microbiome may indicate permeability of external barriers of the body.

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Authors' contribution

Kolesnikova I.M., Karbyshev M.S., Khusnutdinova D.R., Kamaldinova D.R., Borisenko O.V. – analysis and interpretation of the data. Gaponov A.M., Grigoryeva T.V., Makarov V.V. – conception and design, justification of the manuscript or critical revision of the manuscript for important intellectual content. Yudin S.M. – conception and design, final approval of the manuscript for publication. Roumiantsev S.A., Shestopalov A.V. – conception and design, justification of the manuscript or critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication.

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