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FEATURES OF THE ORAL MICROBIOME COMPOSITION IN MEN WITH GASTROESOPHAGEAL REFLUX DISEASE WITH ESOPHAGITIS

This article presents a study conducted to investigate changes in the oral microbiome composition in patients with gastroesophageal reflux disease (GERD) with esophagitis and to identify potential microbiological predictors of complications. A total of 106 patients with a previously verified diagnosis participated. Quantitative real-time PCR was the primary method for assessing the oral microbiome composition. A significant decrease in all phyla of the studied bacteria was found in patients with GERD compared to the control group. The bacterial phyla studied can be used as a predictor of GERD development only in healthy individuals to determine the likelihood of inflammation in healthy mucous membranes, which requires further exploration and study of new biomarkers. The objective of the study was to determine the composition of the oral microbiome in patients with GERD of varying severity and to identify potential microbiological predictors of GERD complications. A total of 106 men aged 35.5±3.4 years were examined, 27 of whom were somatically healthy and 79 of whom were diagnosed with GERD with esophagitis (according to the Los Angeles classification: 26 people with GERD-A, 25 people with GERD-B, and 28 people with GERD-C), who were in remission at the time of examination. A comparison of the oral microbiome status was conducted in healthy men and men with GERD. In patients with GERD-A and GERD-B, reliable differences were found only in relation to bacteria. *Bacteroidetes* – a decrease in their level was noted, *Firmicutes* – an increase in their content in the oral cavity was recorded depending on the severity of GERD, and also phylum *Tenericutes* – an increase in bacterial counts was detected in severe stages of GERD. It is worth noting that patients with GERD-C showed a significant decrease in all phyla of the studied bacteria. The bacterial phyla we studied can be used as a predictor of GERD development only in healthy individuals, to determine the likelihood of GERD with esophagitis.

Keywords: gastroesophageal reflux disease, microbiome, predictor, *Bacteroidetes*, *Firmicutes*, *Tenericutes*

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Introduction. Gastroesophageal reflux disease (GERD) is a chronic polyetiologic disorder characterized by a primary impairment of the motor-evacuation function of the upper gastrointestinal tract (GIT) and the presence of pathological gastroesophageal reflux [2]. According to statistics, both in Russia and worldwide, GERD is one of the leading causes of outpatient medical care for both men and women of young, middle-aged, and elderly age [5]. According to the Russian Ministry of Health, the prevalence of this pathology in the population reaches 13.98% and continues to grow steadily [2]. According to the results of a multicenter study of the prevalence of GERD symptoms in the regions of the Russian Federation, this figure is 34.2%. According to foreign sources, the prevalence of GERD in various countries of the world ranges from 8% to 37% and also shows an upward trend [10]. Due to the increasing frequency of occurrence of the nosology, the presence of complicated forms (esophageal and gastric cancer), as well as extraintestinal manifestations of the disease, such as stomatitis, tonsillitis, chest pain, cough, tooth damage, lesions of the oral mucosa, bronchial asthma, in patients of all age categories, early diagnosis of the disease is becoming especially relevant.

It is known that the adult human body contains 10^{12}–10^{14} different microorganisms. Interaction between the microbiome and the individual occurs in absolutely all structures of the gastrointestinal tract. Special studies have confirmed that certain bacterial strains can cause chronic inflammation of the oral mucosa and the upper gastrointestinal tract (esophagus, stomach, and duodenum). Patients with GERD have a mixed flora, including the oral microbiome (gram-positive bacteria) and gastric microbiome (gram-negative anaerobes), which, as a result of reflux, tends to grow in the mucosa [1, 4]. A number of authors have demonstrated the role of the microbiome in esophageal motor function, including the development of reflux. This is associated with the activation of Toll-like receptors by interaction with lipopolysaccharides of the bacterial cell wall, which entails the activation of nuclear factor and the production of inflammatory cytokines [3, 6, 7].

The aim of our study was to determine the composition of the oral microbiome in patients with GERD and esophagitis of varying severity and to identify possible microbiological predictors of the development of GERD complications.

Materials and methods of research. The study involved 106 men (27 healthy subjects and 79 patients with GERD and esophagitis). All subjects were comparable in age (35.5±3.4 years) and anthropometric characteristics (p>0.05); all had a negative smoking history. All patients provided voluntary informed consent to participate in the study.

Patients with GERD and esophagitis were followed up at the Voronezh City Clinical Polyclinic No. 1, a state-funded healthcare institution in the Voronezh Region. The diagnosis of the underlying disease was verified based on the results of EGD and clinical manifestations (heartburn was observed in 87% of cases (n = 69), chest pain in 51% (n = 40),

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and extraesophageal manifestations in 51% (n = 40)). Patients with GERD with esophagitis were divided into 3 groups according to the Los Angeles classification [10]: GERD-A – one or more areas of mucosal damage in the form of erosion or ulceration less than 5 mm, not extending beyond the mucosal fold (n = 26), GERD-B – one or more areas of mucosal damage more than 5 mm, not extending beyond the mucosal fold (n = 25), GERD-C – damage to two or more mucosal folds, in total occupying less than 75% of the esophageal circumference (n=28). Belonging to the GERD-D group (damage to more than 75% of the mucosal circumference of the esophagus) was an exclusion criterion. Healthy subjects constituted the control group (n = 27). The studied biomaterial was saliva, samples of which were collected in sterile 5 ml tubes 2 hours after the last consumption of food and liquid by the subjects. At the time of biomaterial collection, the patients were not taking any medications and were in remission of the underlying disease. Saliva samples were frozen at -17ºC for up to 4 days and transported to the laboratory under cold chain conditions [8]. The quality of the obtained product was assessed by electrophoresis in 2% agarose gel. DNA extraction was performed using the PROBA-GS reagent kit (DNA-technology, Russia). After centrifugation, the supernatant containing the isolated DNA was transferred to the reaction mixture for PCR amplification. DNA concentration was determined using a Hitachi F-7000 spectrophotometer at a wavelength of 260 nm. The purity of the obtained preparations was judged by the A260/A280 ratio. Quantitative polymerase chain reaction was performed on a Bio-Rad CFX 96 instrument (Bio-rad, USA) using a mixture consisting of 16 µl of water, 5 µl of 5X qPCRmix-HS SYBR (Eurogen, Russia), 1 µl of forward primer, 1 µl of reverse primer, and 2 µl of DNA template. The primers used are presented in Table 1. Comparison of bacterial types was assessed by ΔCT between the control and experimental groups. The average CT value obtained for each pair of primers was converted to a percentage using the following formula:

$$x = \frac{(Eff.Univ)^{CT_{univ}}}{(Eff.Spec)^{CT_{spec}}} \times 100\%$$

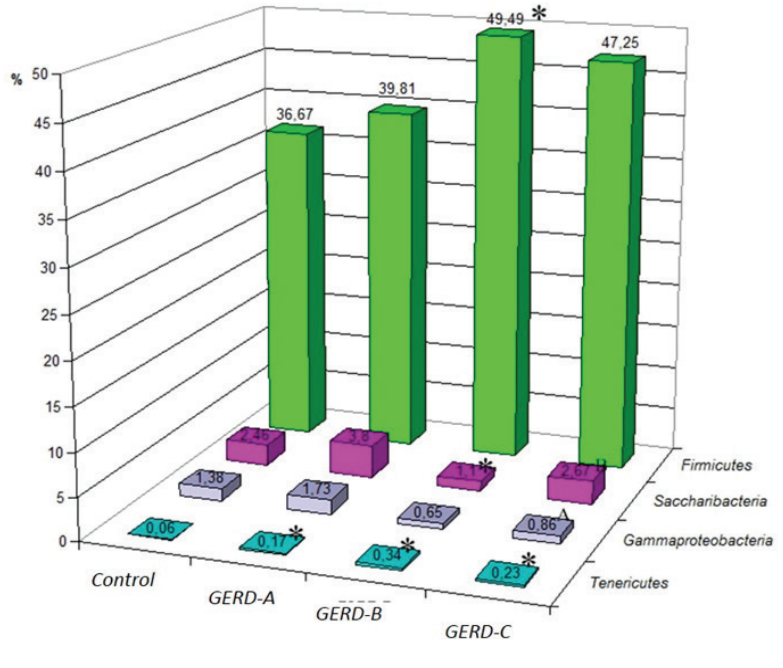
where *Eff.Univ* – estimated efficiency of universal primers (2 = 100% and 1 = 0%); *Eff.Spec* – efficiency of taxon-specific primers; CT_{univ} and CT_{spec} – values *CT*, registered by the amplifier; *x* – proportion of the number of bacteria of a certain type (%).

Statistical processing of the results was carried out using software packages STADIA 8.0 («InCo» (Russia)) and MedCalc 20.104 («MedCalc Software» (Belgium)). The average relative abundance of bacteria of a given phylum in the microbiome, the error of the mean, the standard deviation, the median, and the 95% confidence interval of the mean were calculated. A comparison of the proportions of each phylum in GERD patients and controls was performed using the test χ^2.

Table 1

Pairs of specific primers for microbiome analysis

Type of bacteria	Primer	Primer sequence (5'-3')	Amplicon length (bp)
Bacteroidetes	Bac960F	GTTTAATTCGATGATACGCGAG	122
	Bac1100R	TTAASCCGACACCTCACGG	122
Firmicutes	Firm934F	GGAGYATGTGGTTTAATTCGAAGCA	126
	Firm1060R	AGCTGACGACAACCATGCAC	126
Actinobacteria	Act664F	TGTAGCGGTGGAATGCGC	277
	Act941R	AATTAAGCCACATGCTCCGCT	277
Saccharibacteria	Sac1031F	AAGAGAACTGTGCCTTCGG	187
	Sac1218R	GCGTAAGGGAAATACTGACC	187
Deferribacteres	Defer1115F	CTATTTCCAGTTGCTAACGG	150
	Defer1265R	GAGHTGCTTCCCTCTGATTATG	150
Verrucomicrobia	Ver1165F	TCAKGTCAGTATGGCCCTTAT	97
	Ver1263R	CAGTTTTYAGGATTTCCTCCGCC	97
Tenericutes	Ten662F	ATGTGTAGCGGTAAAATGCGTAA	200
	Ten862R	CMTACTTGCGTACGTACTACT	200
Betaproteobacteria	Beta979F	AACGCGAAAAACCTTACCTACC	174
	Beta1130R	TGCCCTTTCGTAGCAACTAGTG	174
Epsilonproteobacteria	Epsilon940F	TAGGCTTGACATTGATAGAATC	189
	Epsilon1129R	CTTACGAAGGCAGTCTCCTTA	189
Delta and Gammaproteobacteria	Gamma877F	GCTAACGCATTAAGTRYCCCG	189
	Gamma1066R	GCCATGCRGCACCTGTCT	189
Universal	926F	AAACTCAAAKGAATTGACGG	136
	1062R	CTCACRRCACGAGCTGAC	136



Features of the composition of the intestinal microbiome in the study groups

Table 2

Content of some bacterial phyla in individuals with gastroesophageal reflux disease and in control

	Control	GERD-A	GERD-B	GERD-C
Bacteroidetes	50.58±5.39 s_x=25.84 Me=48.46 ДИ=11.04	44.96±6.30 s_x=28.17 Me=47.21 ДИ=13.03	42.76±4.43 s_x=21.23 Me=40.10 ДИ=9.07	43.45±5.52 s_x=25.30 Me=42.66 ДИ=11.38
Firmicutes	36.67±4.57 s_x=21.90 Me=34.43 ДИ=9.36	39.81±6.10 s_x=27.26 Me=37.30 ДИ=12.61	49.49±5.29* s_x=25.38 Me=55.59 ДИ=10.84	47.25±5.25 s_x=24.05 Me=51.94 ДИ=10.82
Actinobacteria	8.64±2.72 s_x=13.04 Me=3.17 ДИ=5.57	9.25±4.18 s_x=18.68 Me=1.28 ДИ=8.64	5.43±2.37 s_x=11.38 Me=1.27 ДИ=4.86	5.50±1.88 s_x=8.60 Me=2.14 ДИ=3.87
Saccharibacteria	2.46±1.34 s_x=6.45 Me=0.81 ДИ=2.76	3.80±1.58 s_x=7.05 Me=1.13 ДИ=3.26	1.10±0.27* s_x=1.31 Me=0.72 ДИ=0.56	2.67±0.74^B s_x=3.33 Me=1.14 ДИ=1.50
Gammaproteo-bacteria	1.38±0.86 s_x=4.13 Me=0.36 ДИ=1.77	1.73±0.82 s_x=3.68 Me=0.19 ДИ=1.70	0.65±0.30 s_x=1.43 Me=0.18 ДИ=0.61	0.86±0.396^A s_x=1.77 Me=0.28 ДИ=0.80
Tenericutes	0.06±0.02 s_x=0.09 Me=0.02 ДИ=0.04	0.17±0.09* s_x=0.39 Me=0.02 ДИ=0.18	0.34±0.32* s_x=1.54 Me=0.003 ДИ=0.66	0.23±0.14* s_x=0.63 Me=0.007 ДИ=0.28
Betaproteo-bacteria	0.23±0.16 s_x=0.80 Me=0.04 ДИ=0.32	0.28±0.19 s_x=0.84 Me=0.05 ДИ=0.39	0.24±0.16 s_x=0.78 Me=0.03 ДИ=0.34	0.12±0.07 s_x=0.31 Me=0.02 ДИ=0.14

Designations: * – differences from the control group are statistically significant (p<0,05);
A – differences from the GERD group-A statistically significant (p<0,05);
B – differences from the GERD group-B statistically significant (p<0,05).

Differences between comparison groups were considered significant when p<0,05.

Results and discussion. An analysis of the oral microbiome was conducted in healthy subjects and those with GERD (Fig. 1, Table 2). It was shown that the predominant bacterial phyla in the oral cavity of both healthy and GERD subjects were *Bacteroidetes* and *Firmicutes* (totaling approximately 90% of the microbiome). A trend toward a decrease in the relative abundance of *Bacteroidetes* bacteria compared to controls was observed in all groups of GERD patients; however, no statistically significant differences were found between the groups. *Bacteroidetes* are able to adapt to low pH conditions. Acid can irritate the mucous membrane and destroy the protective enamel layer, which also facilitates bacterial proliferation [8, 9].

The proportion of *Firmicutes* in patients with GERD-B (49.49%) increased compared to healthy subjects (36.67%). A trend toward an increased relative abundance of *Firmicutes* was observed in patients with GERD-C. Thus, in patients with GERD, there was a redistribution of the proportions of dominant phyla in favor of Firmicutes. This may be due to a change in the pH of the oral cavity toward increased acidity. The change in the abundance of *Firmicutes* is associated with increased acidity in the oral cavity, as these microorganisms prefer a neutral or slightly alkaline environment. With an increase in pH, the activity of antimicrobial components of saliva, peroxidases, and lysozyme decreases, which contributes to a decrease in protection against pathogenic bacteria. Microorganisms in the oral cavity colonize various areas (tooth surfaces, tongue, buccal mucosa, saliva). Saliva plays a crucial role in the colonization of the oral cavity by microorganisms. Not only does it provide a nutrient medium for microbial growth, but it also contains numerous components with antibacterial properties, including antimicrobial peptides, secretory immunoglobulins, lysozyme, and lactoferrin. Catalase, present in saliva, promotes the breakdown of hydrogen peroxide, acting as an antimicrobial protein compared to other well-studied antimicrobial components. These components significantly contribute to the control of microbial communities in the oral cavity and the maintenance of homeostasis, despite the presence of esophagitis, suggesting the development of a compensatory mechanism in the early stages of the disease. The formation of a protective film can facilitate the attachment of various microorganisms and alter the pH of saliva, which minimizes the colonization of pathogenic and opportunistic microorganisms [6, 8, 9, 10].

Microbiome changes were found in patients with GERD regarding the subdominant phyla *Actinobacteria, Saccharibacteria, Gammaproteobacteria, Tenericutes*, and *Betaproteobacteria*. In patients with GERD-B, the proportion of *Saccharibacteria* decreased to 1.10% (compared to 2.46% in controls). Bacteria of this phylum may be associated with inflammation and oral health. Current research suggests that decreased levels of *Saccharibacteria* are a consequence of GERD-induced dysbiosis [8].

In all patients with GERD, the relative abundance of *Tenericutes* significantly exceeded that in healthy individuals (Table 2). This type of bacteria constitutes the majority of oral microorganisms. They play a significant role in the development of periodontal disease—the extraesophageal manifestation of GERD. This may be associated with the release of multiple virulence factors that facilitate tissue penetration, tissue destruction, and disruption of the host immune response. An increase in this phylum is associated with aggressive gastric contents, which determines the severity of GERD [6,7].

For other phyla, no differences in their abundance were found in the microbiomes of healthy individuals and patients with GERD.

Conclusion. It's worth noting that a study of oral microbiome phyla in patients with GERD-C revealed a significant decrease in all phyla of the studied bacteria. This is due to widespread changes in the mucosal layer of the esophagus and oral cavity, which leads to the inability of these bacteria's compensatory mechanisms to function due to constant exposure to acidic contents due to reflux from the stomach. Therefore, the bacterial phyla we studied can be used as a predictor of GERD development only in healthy individuals, to determine the likelihood of inflammation occurring in healthy mucosa, which requires further exploration and study of new biomarkers.

The oral microbiome is directly linked to the development of upper gastrointestinal diseases associated with reflux lesions, which may be a promising direction in differentiating at-risk patients

before endoscopic screening at the outpatient stage.

The authors declare no conflict of interest.

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VARIABILITY OF PNPLA3 AND GCKR GENES, AND THEIR INFLUENCE ON BIOCHEMICAL PARAMETERS IN RESIDENTS OF THE REPUBLIC OF SAKHA (YAKUTIA)

The article presents a study of the frequencies of *PNPLA3* and *GCKR* gene variants in samples of Yakuts, Evenks, and Russians. A total of 728 people living in the Sakha Republic (Yakutia) participated (331 Yakuts, 147 Evenks, and 250 Russians). Single nucleotide polymorphisms were determined by polymerase chain reaction followed by restriction fragment length polymorphism analysis. The study revealed significant differences between the studied samples. For the rs738409 polymorphism of the *PNPLA3* gene, the G allele was 72-75% in Yakuts and Evenks versus 53% in Russians. For the rs2294918 polymorphism, the protective allele A is virtually absent in Yakuts (6.7%) and very rare in Evenks (17%), the Russian population has a significantly higher proportion of A (43%). For rs1260326 of the *GCKR* gene, the risk allele T was more common in Russians than in Yakuts and Evenks. For the associated SNP rs780094, Russians have a higher percentage of the risk allele A, approximately 48% versus 40% in Yakuts and 44% in Evenks. Linkage disequilibrium (LD) analysis between the pair of polymorphisms rs738409 and rs2294918 in the *PNPLA3* gene showed an extremely weak association between these SNPs. Polymorphisms rs780094 and rs1260326 *GCKR* demonstrated strong linkage in all three studied samples. In the Russian sample, an association was noted between the genotype of the rs738409 *PNPLA3* polymorphism and the concentration of triglycerides, and polymorphisms of the *GCKR* gene showed a significant effect on ALT activity. The obtained data are consistent with the hypothesis that some pathological alleles became established in northern populations due to previous adaptive advantages, but in modern conditions, they have transformed from beneficial to harmful.

Keywords: *PNPLA3, GCKR, NAFLD,* Yakuts, Evenks, Russians

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