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Comparative analysis of the oral cavity microflora state in various degrees of inflammatory conditions of periodontal tissues using comprehensive studies

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Abstract

The authors conducted a comparative analysis of the frequency of occurrence of various bacterial pathogens in the oral cavity (OC) and their role in the etiology of periodontal complex diseases in patients with periodontitis of varying severity and a control group (CG) of healthy individuals. The study results demonstrated that significant changes in the periodontal complex microflora were more frequently observed in individuals with various inflammatory periodontal diseases. These changes were detected using classical and modern methods to study the composition of the microflora of the oral mucosa (OM) and gums. The findings showed an increase in both periodontopathogenic agents and pathogenic coccal flora. According to the authors, the combination of microorganisms from the "red complex" with Streptococcus pyogenes and Staphylococcus aureus contributes to biofilm formation and a higher risk of exopolymeric matrix destruction, which corresponds to the clinical manifestations and severity of periodontitis progression.

Keywords: Anaerobic and aerobic microbes, Dentistry, Oral microflora, Periodontitis, Periodontogenic microorganisms.

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1. Introduction

Relevance. It is known that the oral cavity (OC) serves as a favorable environment for the proliferation and biological activity of numerous microorganisms [1-3]. In this context, along with the positive symbiotic interactions with the soft tissues of the periodontal complex, the negative effects of representatives of the normal microflora are also observed [4-6]. A prominent example of this is the most well-known large group of the OC microbiota—facultative anaerobes, which include highly pathogenic Staphylococci and Streptococci [7-9]. Moreover, there is a growing body of evidence regarding the role of pathogenic Staphylococci and β-hemolytic Streptococci in various OC pathologies [10, 11]. Scientific research on the etiopathogenesis of inflammatory periodontal diseases (IPD) in dentistry, including studies related to microbiotic analysis in normal and pathological conditions [12, 13], highlights the significance of obligate/facultative aerobic and anaerobic microorganisms in various pathologies of the oral biome (OB). These microorganisms are reported to contribute to purulent inflammation of periodontal tissues (PT) and oncological changes [14, 15]. Additionally, studies discuss the diversity of the oral mucosa (OM) microbiome, which is influenced by factors such as the human living environment, geography, and exposure to unfavorable industrial conditions. Other contributing factors include the uniqueness of the ecosystem, regional characteristics, ethnogeography, dietary culture, and oral hygiene practices [16, 17]. However, due to the lack of sufficient research on the etiopathogenesis of oral diseases and the role of various microorganisms in the population of Central Asia, there is a critical need for comprehensive studies using microbiological and molecular research methods to investigate the etiology of periodontal complex diseases [18, 19].

The aim of the study: To determine the frequency of occurrence and etiopathogenetic significance of key microbiota present in the oral cavity among healthy individuals (control group - CG) and patients with various forms of periodontitis.

2. Materials and Methods

This scientific study was conducted in 2023 at the Department of "Dentistry, Pediatric Dentistry, and Orthodontics" of CDQPMW. Samples were collected from the periodontal tissue (PT) complex of patients with purulent inflammatory periodontal diseases (IPD) who sought dental care. Comprehensive microbiological studies were performed using classical and modern methods. To achieve this, samples from various areas of the oral cavity (OC) were analyzed for the presence and ecological role of obligate and facultative anaerobic microorganisms, including *Streptococcaceae, Staphylococcaceae, Neisseriaceae, Corynebacteriaceae, Haemophilus spp., Enterobacteriaceae, Klebsiella spp., Pseudomonas aeruginosa, and Candida spp.* Additionally, molecular-genetic analyses were conducted to detect *Actinobacillus/Aggregatibacter actinomycetemcomitans, Treponema denticola, Prevotella intermedia, Tannerella forsythensis, Porphyromonas gingivalis*, and Candida albicans, among others. Enriched and selective nutrient media were used for cultivation, considering the microorganisms' ecological niches and environmental conditions. In the study, a targeted main group (MG-1) consisting of 112 patients with periodontitis and a control group (CG - Group II) of 40 healthy individuals aged 30-55 underwent comprehensive examinations to assess the condition of the oral cavity (OC). During patient evaluations, key clinical criteria for periodontal tissue (PT) assessment included hyperemia, swelling, hygiene status, coloration of the oral mucosa (OM), and other visual indicators of periodontal complex pathology. These parameters were assessed using traditional methods and included indices such as the Gingival Index (GI), Papillary-Marginal-Attached Index (PMA), Periodontal Index (PI), and Community Periodontal Index of Treatment Needs (CPITN).

3. Results

During the study period, the gender distribution among the examined patients was as follows: 60.7% (68 individuals) were female, and 39.3% (44 individuals) were male. Among the healthy individuals in the control group, 67.7% (27 individuals) were female, while 32.3% (13 individuals) were male (Figure 1).

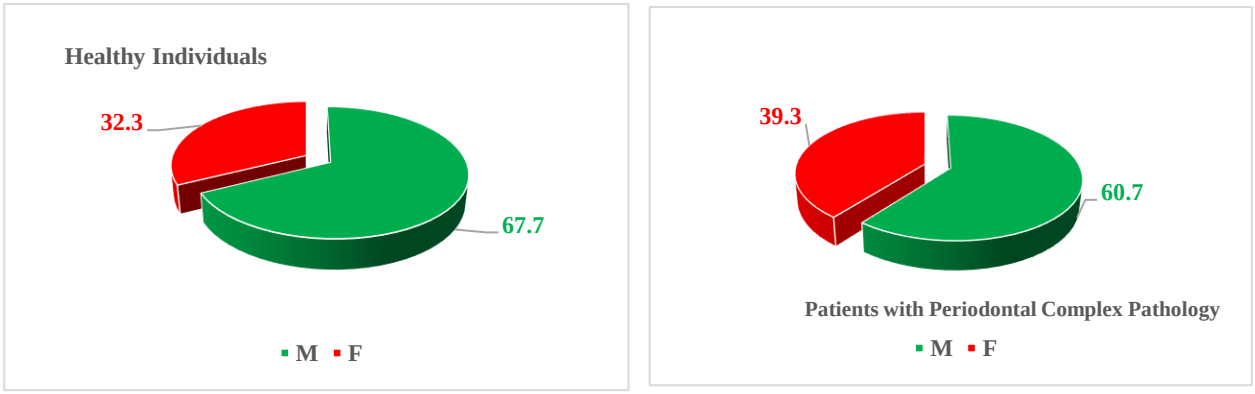


Figure 1.
Gender Distribution of Study Participants.

The results of the study revealed that the biological samples from the examined individuals contained not only representatives of the normal flora, such as the *Streptococcaceae* family (including the “Viridans” group of green streptococci: *Streptococcus mitis, Streptococcus mutans, Streptococcus oralis, Streptococcus sanguinis, Streptococcus sobrinus*, and the *Streptococcus anginosus* group), *Staphylococcaceae, Neisseriaceae, Corynebacteriaceae*, and *Haemophilus spp.*, but also

Gram-negative bacteria. These included non-fermenting Gram-negative bacteria from the *Enterobacteriaceae* family, such as *Klebsiella spp.*, *Pseudomonas aeruginosa*, and *Candida spp.* (Table 1).

Table 1.
The frequency of occurrence of facultative anaerobic microorganisms in the oral mucosa among the examined individuals.

No	Family/genus	Microorganism type	Frequency of occurrence (abs.%)	
			1 - gr. n=112	2 - gr. n=40
1	Staphylococcaceae\ Staphylococcus	Coagulase-positive staphylococci, including *S. aureus*	35 (31,3)	8 (20,0)
		Coagulase-negative staphylococci	14 (12,5%)	15(37,5%)
2	Streptococcaceae\ Streptococcus	α-hemolytic streptococci (Viridans group streptococci - VGS)	108 (96,4%)	40 (100%)
		β-hemolytic streptococci, including *S. pyogenes*	32 (28,6%)	2 (5,0%)
3	Neisseriaceae\ Neisseriae	N. meningitidis	0	0
		Non-pathogenic Neisseria species	95 (84,8%)	38(95,0%)
4	Pasteurellaceae Haemophilus	Haemophilus influenzae	0	0
		Non-pathogenic Haemophilus species	35 (31,3%)	38(95,0%)
5	Corynebacteriaceae\ Corynebacterium	C. diphtheriae	0	0
		Non-pathogenic Corynebacterium species	92 (82,1%)	35 (87,5%)
6	Enterobacteriaceae	Enterobacteriaceae spp , including Klebsiella spp	2 (1,8%)	0
7	Bifidobacterium	Bifidobacterium spp	42 (37,5%)	34 (85,0%)
8	Lactobacillaceae\ Lactobacillus	Lactobacillus spp	33 (29,5%)	33 (82,5%)
9	NGOB	Pseudomonas aeruginosa	1 (0,9%)	0
10	Candida spp.	Candida spp.	38 (33,9%)	5(12,5%)

In particular, the growth characteristics of the cultures, colony morphology, the presence of α and β hemolysis, the production of certain enzymes responsible for pathogenic traits (lecithinase), staining properties, and other indicators were evaluated. Bacteria that grew to more than 50% of the total microorganisms were considered dominant, and subsequent identification through mass spectrometry revealed significant differences between the two groups, particularly with Gram-positive (Gram+) cocci flora. Pathogenic isolates not only demonstrated dominance among coagulase-positive staphylococci but also among β-hemolytic streptococci. In this case, considering the potential risk of "healthy carriers" in the pathogenic group of cocci flora, negligence in dental practice may lead to the development of inflammatory processes (IP) in the upper respiratory tract, and, in combination with other pathogens, can cause abscesses or phlegmon in the facial area (FA), resulting in severe outcomes, including fatal complications.

In the next phase of the study, the differences between the two groups were assessed based on the biological characteristics of the pathogenic cocci. Coagulase-positive (coagulase+) staphylococci, mainly *S. aureus*, were found to exhibit varying levels of pathogenicity and differing sensitivity to antibacterial agents. Non-pathogenic *Haemophilus*, *Corynebacterium*, and *Neisseria* species were more commonly found in healthy individuals (CG) ($P<0.05$), with no growth of pathogenic variants observed.

To isolate pneumococci, gentamicin and optochin discs were added to the initial culture media. In the first stage, *Streptococcus pneumoniae* was distinguished from other α-hemolytic streptococci, and its growth was observed, which accelerated diagnostic capabilities.

Throughout the study, the biological characteristics, cultural, and biochemical traits of the isolated non-pathogenic *Neisseria*, *Haemophilus*, and *Corynebacterium* species were consistent with descriptions from various sources.

Using the MALDI-TOF MS mass spectrometry method, the isolates that were presumed to be staphylococci and grew in the culture medium (CMS) were differentiated using a DNA test (Deoxyribonuclease activity). The presence of the DNase enzyme, along with the plasmacoagulase enzyme in the isolated strain, was found to be of significant diagnostic importance and one of the main factors in the pathogenicity of staphylococci. Along with Staphylococcus aureus, Staphylococcus caprae (coagulase-negative (-) staphylococci) also exhibited DNase activity. This test helped in differentiating closely related pathogens, including the Klebsiella-Enterobacter-Serratia group from the Enterobacteriaceae family and in screening C. diphtheriae.

Undoubtedly, the use of MALDI-TOF MS, or other bacteriological analyzers based on biochemical characteristics (such as VITEK MS and The BD Phoenix™ M50), along with the DNAse Test Agar, facilitated the identification of pathogenic microorganisms.

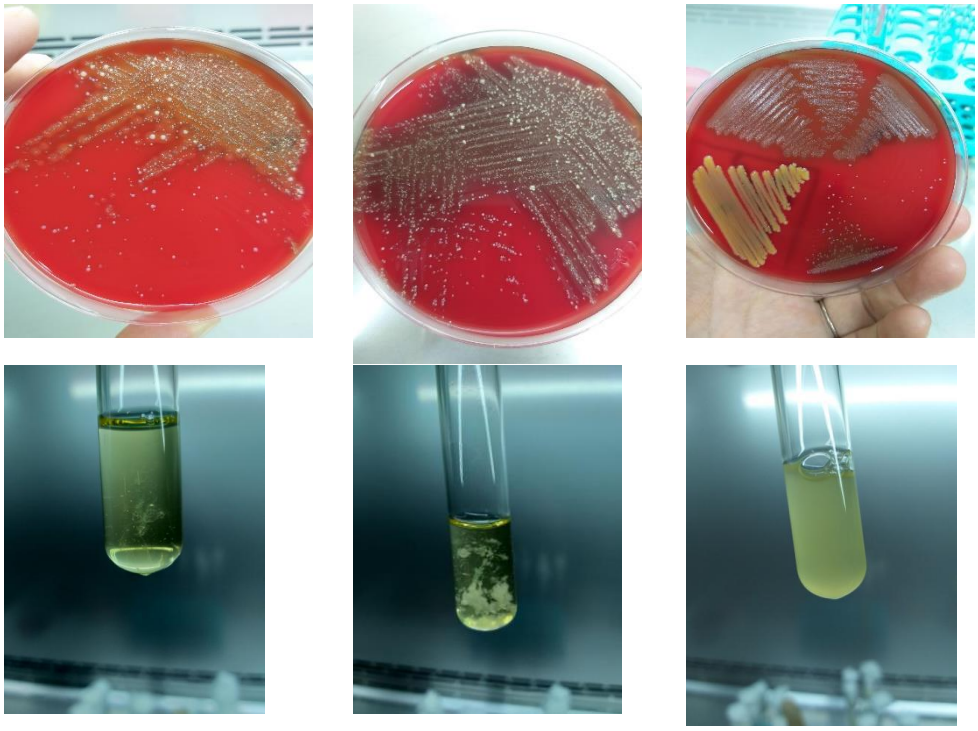
The results revealed that after accurate identification of the *Staphylococcaceae* and *Streptococcaceae* families, *S. aureus* was dominant among patients, with 35 isolates (31.3%), while in the healthy group, 8 isolates (20.0%) were found. Among them, α-hemolytic streptococci were dominant, occurring at high titers in 96.4% to 100%, indicating that this is normal (except for *Streptococcus pneumoniae*).

During the study, all samples of β-hemolytic streptococci amounted to 34 isolates, of which 31 strains were initially identified as Streptococcus pyogenes. Three isolates exhibited atypical characteristics, and their species could not be determined using classical methods. For identifying the remaining β-hemolytic streptococci, the "Sherman test" was used (Figure 2).

Figure 2.
Identification results of the main representatives of *Streptococccaceae* and *Staphylococcaceae* species using classical methods.

The identification of streptococci using classical methods involves biochemical features based on enzymatic characteristics and serological indications based on the polysaccharides in the cell wall of streptococci (Lancefield Classification). Among the β-hemolytic streptococci, the following clinically significant species were observed (Figure 3):

- Group A: *S. pyogenes*
- Group B: *S. agalactiae*
- Group C: *S. dysgalactiae* (rarely *S. equi*)
- Group G: *S. dysgalactiae*, *S. canis*, and others.



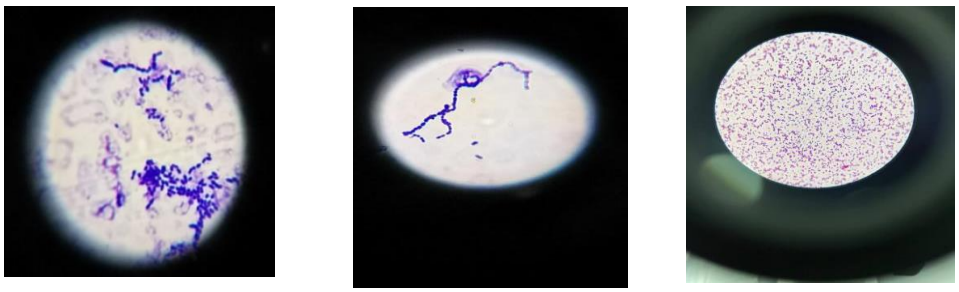


Figure 3.
Identification results of the main representatives of *Streptococcus* species from *Streptococcus pyogenes* using classical methods.

Three isolates, identified using mass spectrometry, were all found to be Streptococcus anginosus with β-hemolytic characteristics. It is known that in modern classification, Streptococcus anginosus forms a group with Streptococcus intermedius and Streptococcus constellatus, and data confirm that 25% of S. constellatus isolates exhibit β-hemolytic properties. Additionally, these species can sometimes become harmful pathogens, potentially causing brain and liver abscesses, which highlights the importance of specialist diagnostics in dental practice.

The representatives of Enterobacteriaceae and NGOB were identified using classical methods, including the characteristic growth of lactose-positive colonies on Endo agar, followed by inoculation onto combined carbohydrate media (KLIGLER agar). The enzymatic properties of the obtained gram-negative microorganisms were then studied through the "colored" series. The results showed that the following representatives of obligate anaerobic microorganisms were observed as the main pathogens of periodontal tissues (Table 2).

Table 2.
The bacterial complex composition identified in the process of periodontal tissue inflammation.

№	Genus/species affiliation of microorganisms	Microbiological characteristics
1.	Actinomyces odontolyticus	The filamentous shape of facultative anaerobic Gram (+) bacteria
2.	Veillonella parvula	Gram (-) coccobacilli, obligate anaerobes
3.	Streptococcus mitis,	Facultative anaerobic Gram (+) coccoid-shaped bacteria (forming chains of varying lengths)
4.	Streptococcus israilis,	
5.	Streptococcus sanguis and others (Streptococcus: gordonii, intermedius)	
6.	Aggregatibacter (Actinobacillus) actonomycetemcomitans	Gram (-) coccobacilli, facultative anaerobes
7.	Capnocytophaga spp.	Gram (-) polymorphic rod-shaped bacteria, microaerophiles.
8.	Eikenella corrodens	Gram (-) rod, coccobacillus, facultative anaerobe.
9.	Campylobacter concisus	Gram (-) curved bacteria, microaerophilic (fastidious).
10.	Campylobacter rectus	Gram (-) slightly curved rods, facultative anaerobe (microaerophilic).
11.	Fusobacterium nucleatum	Gram (-) rods, obligate anaerobes.
12.	Peptostreptococcus micros	Gram (+) coccoid-shaped bacteria arranged in chains, obligate anaerobes.
13.	Prevotella intermedia; Prevotella nigrescens	Gram (-) coccobacillus, obligate anaerobe.
14.	Tannerella forsythia	Gram (-) slightly curved rods, obligate anaerobes.
15.	Treponema denticola	Gram (-) slightly curved rods, spirochetes, obligate anaerobes.
16.	Porphyromonas gingivalis	Gram (-) short rods, obligate anaerobes.
Complex names: Purple; Yellow ; Green Orange; Red		

The results obtained in Table 2 are based on the study of dominant microorganisms in various inflammatory processes of periodontal pathogens' microflora, based on the complex theory and criteria of periodontal pathogens [20].

Based on the above results and analyses, in our research, we identified and evaluated the etiological significance of anaerobes - *Actinobacillus/Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Prevotella intermedia*, *Tannerella forsythensis*, *Porphyromonas gingivalis*, and *Candida albicans* using molecular-genetic methods. For this, a specially enriched base medium was used in the initial cultivation phase, and significant microorganisms were grown under anaerobic conditions.

The conducted studies revealed significant differences between the two groups, with more facultative anaerobic microorganisms, including pathogenic cocci and obligate anaerobes ($n<0.05$) (Figure 4). The classification of some obligate anaerobes into their respective genera, as well as the identification of microorganisms using classical methods and studying

their cultural and tintorial characteristics, allowed for the determination of their genus and species affiliations through simple biochemical tests and mass spectrometry techniques.

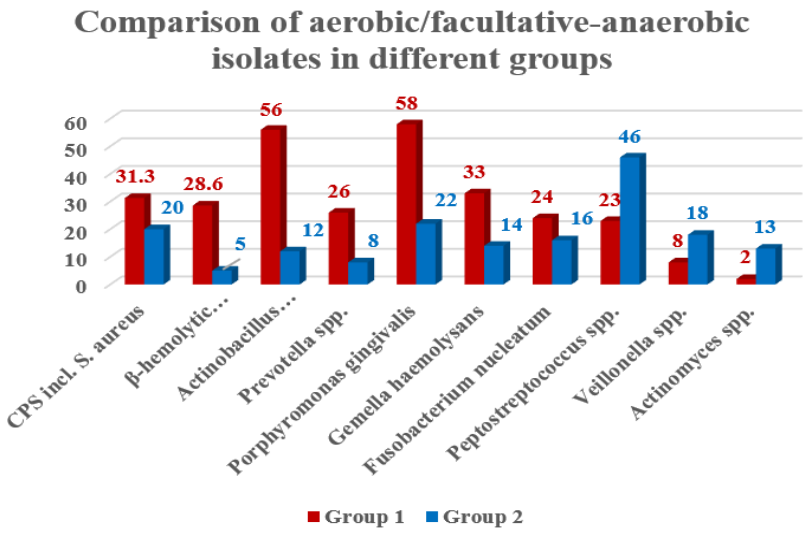


Figure 4.
Comparison of aerobic/facultative-anaerobic isolates in different groups.

The results show that pathogenic obligate anaerobes were more frequently isolated from group MG-1, with representatives of Porphyromonas gingivalis (58%/65%), *Actinobacillus actinomycetemcomitans/Aggregatibacter actinomycetemcomitans* (56%/63%), Fusobacterium nucleatum (24%/27%), Prevotella spp. (26%/29%), and Peptostreptococcus spp. (23%/26%). A large proportion of *Peptostreptococcus* micros were found to be associated with this group. On the other hand, Peptostreptococcus spp. (46%/18%), Veillonella spp. (18%/7%), and Actinomyces spp. (13%/5%) were more prevalent in the healthy individuals (CG) group. Additionally, among the obligate anaerobes, P. gingivalis and T. denticola, both with aggressive properties, were identified as playing an active role in periodontal bleeding and tissue destruction.

In laboratory practice, molecular-genetic research, specifically PCR, was used to study biological material, where primers and probes were employed to isolate the total DNA of *Prevotella intermedia*, *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythensis*, *Treponema denticola*, and Candida albicans. This approach allows for the detection of pathogenic differences in the mixed composition of periodontal pocket microorganisms, which serve as the cause of periodontal diseases, distinguishing it from a normal state. The comparative analysis of the periodontal microbiota composition in the biological samples revealed that the presence of obligate anaerobic flora was significantly higher. Furthermore, the encounter frequency of six microorganisms in both groups showed statistically significant differences ($P < 0.05$).

The data obtained indicate that the total bacterial mass in the KG samples ranges from 3.5 to 6.0 Lg. In patients with varying degrees of periodontal disease (РЯК), this figure was found to be between 7.5 and 9.8 Lg. In the total mass, the encounter frequency of *Actinobacillus actinomycetemcomitans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, *Tannerella forsythensis*, and Treponema denticola was significantly higher in comparison to the "healthy" individuals' CG (Figure 5).

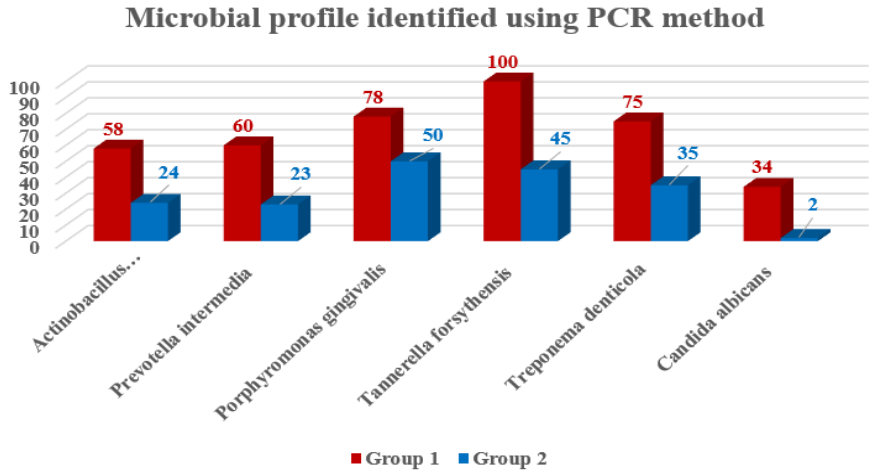


Figure 5.
Microbial profile identified using PCR method.

In addition to the main bacterial pathogens, the identification of microscopic fungi of the Candida spp. genus was possible using a test kit method, which, alongside Gram-positive flora, also allowed for the detection of Gram-negative flora, considered some of the most demanding periodontal microorganisms. The identification of the presence of these microorganisms in biological samples, as well as the simultaneous occurrence of facultative anaerobes, obligate anaerobes, and yeast-like microscopic fungi, is of significant importance in practical dentistry. Adequate treatment of purulent periodontal diseases, one of the most complex problems in therapeutic dentistry, requires a comprehensive approach to determine the etiopathogenesis of diseases associated with oral and systemic conditions.

4. Conclusions

1. In the study, changes in the periodontal complex microflora were more frequently observed in individuals with various forms of periodontal diseases, with an increase in the number of periodontal pathogenic agents (Porphyromonas endodontalis, Treponema denticola, Tannerella forsythia, Prevotella intermedia, Fusobacterium nucleatum) and Candida albicans, as well as pathogenic representatives of Streptococcus and Staphylococcus species.
2. The presence of Aggregatibacter actinomycetemcomitans, along with "red complex" microorganisms such as Porphyromonas gingivalis, Tannerella forsythia, as well as St. pyogenes and St. aureus, contributes to the formation of biofilms and increases the risk of disruption of the exopolymeric matrix, which corresponds to the severity levels of the periodontal disease process.
3. The results of microbiological studies show that the use of both classic and molecular-genetic methods enhances the diagnostic accuracy of identifying the mixed microbial composition of periodontal pocket microorganisms, revealing individual differences in the frequency of microorganism encounters. In this case, combining these two methods in laboratory practice provides the opportunity to gather regional data on major pathogens.

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