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THE RELATIONSHIP BETWEEN THE ORAL MICROBIOTA AND THE DEVELOPMENT OF DENTAL CARIES

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Abstract: The oral cavity is one of the most complex microbial ecosystems in the human body, harboring more than 700 bacterial species, as well as fungi, viruses, archaea, and protozoa. In recent years, advances in molecular biology, metagenomics, and 16S rRNA sequencing technologies have fundamentally changed classical views on the etiology of dental caries. According to the modern scientific concept, dental caries is not caused by a single pathogenic microorganism, but is a multifactorial disease that develops as a result of dysbiosis of the oral microbiota, changes in biofilm composition, and disruption of ecological balance. This article analyzes the composition of the oral microbiota, biofilm formation, microbial interactions involved in the development of dental caries, molecular mechanisms, and promising directions for microbiome-based prevention and treatment on the basis of contemporary scientific literature. Recent systematic reviews indicate that there are both taxonomic and functional differences between the microbiota of healthy individuals and individuals affected by dental caries, while the main underlying mechanism of the disease is considered to be microbial dysbiosis.

Keywords: oral microbiota, microbiome, dental caries, biofilm, dysbiosis, Streptococcus mutans, ecological plaque hypothesis, metagenomics, 16S rRNA.

INTRODUCTION

Dental caries is one of the most prevalent chronic diseases worldwide. It affects individuals across all age groups and is one of the major reasons for seeking dental care. Over the past several decades, scientific approaches to the study of dental caries have undergone significant development. Whereas Streptococcus mutans was previously considered the primary causative agent, dental caries is now regarded as a complex multifactorial disease resulting from disruption of the ecological balance of the oral microbiota. The oral microbiota is one of the most complex microbial communities in the human body, second only to the intestinal microbiota in terms of complexity. It consists of bacteria, fungi, viruses, archaea, and other microorganisms. More than 700 microbial species have currently been identified in the human oral cavity, most of which coexist in symbiotic relationships. These microorganisms play an important role not only in maintaining oral health but also in local immunity, metabolic processes, and overall human health. The development of microbiological research has gradually changed our understanding of the etiopathogenesis of dental caries. The non-specific plaque hypothesis initially proposed by Miller, the specific plaque hypothesis later introduced by Loesche, and finally the ecological plaque hypothesis developed by Marsh formed the basis of the modern concept of caries development. According to current scientific views, dental caries is not simply the result of the activity of one or two bacterial species, but rather a consequence of disruption of the ecological balance among microorganisms within the biofilm. High-throughput molecular techniques such as metagenomics, transcriptomics, and metabolomics have demonstrated the involvement of

numerous microorganisms that were previously unknown or underestimated in the development of dental caries. In particular, Streptococcus mutans, Streptococcus sobrinus, Scardovia wiggsiae, Veillonella spp., Actinomyces spp., Lactobacillus spp., Prevotella spp., and many other microorganisms have been shown to interact functionally in shaping the cariogenic properties of dental biofilms [1]. Recent systematic reviews demonstrate that the oral microbiota of healthy individuals and individuals with dental caries differs not only in taxonomic composition but also in metabolic activity. An increased proportion of acid-producing and acid-tolerant microorganisms leads to a reduction in biofilm pH, enamel demineralization, and the development of dental caries. Therefore, the current approach to the prevention and treatment of dental caries focuses not only on eliminating pathogenic bacteria but also on restoring the physiological balance of the oral microbiota. Probiotics, prebiotics, postbiotics, and novel biological technologies aimed at modulating the microbiome are considered promising approaches in this field. The oral cavity is one of the most complex and dynamic microbial ecosystems in the human body. According to modern molecular genetic studies, more than 700 bacterial species have been identified in the oral cavity. Approximately half of them can be cultivated under laboratory conditions, whereas the remainder can only be detected using metagenomic methods [2]. In a healthy oral cavity, microorganisms coexist in a state of physiological equilibrium. This balance is referred to as microbial homeostasis. Salivary composition, local immunity, pH, dietary habits, and biofilm composition play important roles in maintaining this homeostasis [6]. The major bacterial genera of the oral microbiota include Streptococcus, Actinomyces, Veillonella, Neisseria, Rothia, Haemophilus, Prevotella, Fusobacterium, Porphyromonas, and Lactobacillus. Under healthy conditions, these microorganisms coexist through competitive and cooperative interactions, thereby limiting the excessive proliferation of pathogenic bacteria. Consequently, modern scientific approaches regard the oral microbiota not merely as a collection of microorganisms but as a complex ecological system [3, 4]. Dental biofilm plays a central role in the development of dental caries. Biofilm is a complex biological structure composed of microorganisms attached to the tooth surface, polysaccharides, proteins, and an extracellular matrix. Biofilm formation occurs in several stages.

Stage 1. Pellicle formation

Within several minutes after the tooth surface is cleaned, an acquired pellicle consisting of salivary glycoproteins, statherin, proline-rich proteins, and enzymes is formed [5]. This pellicle serves as a receptor and attachment surface for microorganisms.

Stage 2. Initial colonization

Gram-positive facultative anaerobic bacteria are among the first microorganisms to attach to the tooth surface. These include Streptococcus sanguinis, Streptococcus mitis, Streptococcus oralis, and Actinomyces naeslundii. They firmly attach to the pellicle through adhesin proteins [6].

Stage 3. Biofilm maturation

Following the initial colonizers, secondary microorganisms attach to the developing biofilm. These include Veillonella spp., Fusobacterium nucleatum, Prevotella spp., and Capnocytophaga spp. Fusobacterium nucleatum acts as a “bridging bacterium” within the biofilm, connecting aerobic and anaerobic microorganisms [7].

Stage 4. Formation of the Extracellular Matrix

A substantial part of the biofilm consists not of bacterial cells themselves but of polysaccharides produced by the microorganisms. S. mutans utilizes sucrose and, through glycosyltransferase enzymes, produces glucans, fructans, and dextrans. These polysaccharides strengthen the biofilm and protect bacteria from mechanical and immune-mediated effects [8]. Frequent consumption of fermentable carbohydrates, particularly sucrose, leads to ecological changes within the biofilm. Fermentation of carbohydrates by biofilm microorganisms increases, resulting in enhanced production of organic acids. Consequently, biofilm pH falls below the critical level and the proportion of acid-tolerant (aciduric)

bacteria increases. As a result, enamel demineralization is accelerated and the caries process develops [9].

Key Cariogenic Properties of Streptococcus mutans

1. **Strong adhesion -** Antigen I/II proteins facilitate bacterial attachment to the tooth surface.

2. Glycosyltransferase enzymes - GtfB, GtfC, and GtfD enzymes synthesize insoluble glucans, resulting in thickening of the biofilm.

3. Acid production - Glucose is metabolized into lactic acid, acetic acid, and formic acid. Biofilm pH may frequently fall below 5.5, leading to dissolution of hydroxyapatite crystals in dental enamel [10].

4. Aciduricity - S. mutans can survive under low-pH conditions. The F-ATPase enzyme system helps maintain intracellular pH homeostasis.

Consequently, even when other bacteria are inhibited or eliminated, S. mutans may continue to remain metabolically active. Is dental caries simply a disease caused by s. Mutans? Recent metagenomic studies have demonstrated that dental caries is a polymicrobial disease. The following microorganisms have also been detected in high abundance in carious lesions: scardovia wiggsiae, bifidobacterium dentium, lactobacillus fermentum, veillonella dispar, prevotella histicola, actinomyces gerencseriae. Therefore, the modern scientific literature increasingly favors the microbial dysbiosis model rather than the traditional "S. mutans theory" [12, 13]. Traditional microbiological methods allow the identification only of microorganisms capable of growing on artificial culture media. However, a substantial proportion of the oral microbiota cannot be cultivated under standard laboratory conditions. Consequently, advances in molecular biology have initiated a new era in microbiome research [11]. The 16S rRNA gene is a conserved gene found in bacteria, while its hypervariable regions (V1–V9) enable bacterial identification at the species level and, in some cases, at the strain level. This method allows the bacterial diversity of the oral cavity to be assessed with high precision. The main advantages of 16S rRNA sequencing include:

- identification of microorganisms that cannot be cultured in the laboratory;
- comprehensive assessment of microbiota composition;
- determination of the relative abundance of bacterial taxa;
- comparison of healthy and caries-associated biofilms;
- assessment of the degree of dysbiosis.

Using this technology, researchers have demonstrated significant alterations in the composition of the oral microbiota in patients with dental caries compared with healthy individuals. In particular, an increased proportion of acid-producing and acid-tolerant bacteria has been identified as one of the major microbiological characteristics of the disease [1]. While 16S rRNA sequencing is primarily used to characterize bacterial composition, shotgun metagenomics enables comprehensive analysis of all genetic material within the biofilm. This approach can assess: bacteria, viruses, fungi, archaea, antibiotic resistance genes, metabolic pathways, virulence factors. Shotgun metagenomic studies indicate that not only the abundance of bacteria but also their functional activity is important in the development of dental caries. For example, the expression of genes involved in carbohydrate metabolism, polysaccharide synthesis, and organic acid production is considerably higher in carious lesions [14]. Not all genes within the microbiome are equally active. Therefore, metatranscriptomics enables the identification of actively expressed genes. This approach can assess: microbial metabolic activity, intercellular signaling within biofilms, expression of acid-producing enzymes, stress-response mechanisms, activity of virulence factors. This method is considered a promising diagnostic tool for detecting early stages of dental caries [15]. Metabolomics investigates small-molecule metabolites produced by microorganisms. The following metabolites are particularly important in the development of dental caries: lactic acid, acetic acid, propionate, butyrate, pyruvate, ammonia, hydrogen peroxide.

In healthy biofilms, alkaline metabolites are relatively more abundant, whereas in caries-associated biofilms, the concentration of organic acids increases substantially. As a result, biofilm pH falls below the critical level, initiating enamel demineralization [12]. In recent years, considerable interest has been directed toward the study of the salivary microbiota. Saliva sampling is a non-invasive, simple, and patient-friendly method. Scientific studies indicate that certain microorganisms and metabolites present in saliva may allow the risk of dental caries to be assessed in advance. Potential biomarkers include: streptococcus mutans, scardovia wiggsiae, veillonella parvula, lactobacillus spp., lactic acid, glycosyltransferase enzymes. In the future, rapid screening tests based on these biomarkers may be developed [14]. In recent years, the concept of dental caries treatment has undergone substantial changes. The primary goal is no longer to eliminate all bacteria but rather to restore microbial balance.

Probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to the host. The following probiotic strains have been extensively studied in dentistry: lacticaseibacillus rhamnosus GG, limosilactobacillus reuteri, streptococcus salivarius K12, streptococcus salivarius M18, lacticaseibacillus paracasei. Their major mechanisms of action include: competition with pathogenic bacteria for receptors and adhesion sites, production of bacteriocins, modification of biofilm composition, stimulation of the local immune response, normalization of pH. Several clinical studies have demonstrated that probiotic administration may reduce the abundance of S. mutans and decrease the risk of developing new carious lesions. However, additional randomized clinical trials are required to determine the optimal strains, dosage, and duration of administration [15].

Prebiotics are substrates that promote the growth of beneficial microorganisms. In the oral cavity, prebiotics may: support the development of a healthy microbiota, reduce the cariogenic properties of biofilms, limit acid production, stimulate the metabolism of beneficial bacteria. When used together with probiotics, they may exert a synbiotic effect [6].

Postbiotics are biologically active metabolites or cellular components produced by beneficial microorganisms. Promising postbiotics in dentistry include: bacteriocins, short-chain fatty acids, enzymes, peptides, cell wall fragments. An important advantage of postbiotics is that they may allow modulation of the microbiota without the administration of live bacteria, making them a promising approach from a safety perspective [11].

DISCUSSION

Over the past two decades, research into the oral microbiota has substantially changed our understanding of the etiopathogenesis of dental caries. While dental caries was previously associated primarily with the activity of Streptococcus mutans, modern molecular genetic studies indicate that the disease develops as a result of polymicrobial dysbiosis. Next-generation sequencing (NGS), 16S rRNA sequencing, and metagenomic analyses have demonstrated significant differences in both the composition and functional activity of the microbiota between individuals with dental caries and healthy individuals. In particular, disruption of the ecological balance within the biofilm and an increased proportion of acid-producing and acid-tolerant microorganisms are now recognized as major microbiological mechanisms underlying enamel demineralization. Microorganisms within the biofilm interact through metabolic cooperation. For example, species of Veillonella utilize organic acids produced by streptococci as metabolic substrates, while Fusobacterium nucleatum acts as a “bridge” connecting different bacterial species. Therefore, explaining the development of dental caries solely in terms of a single microorganism is scientifically insufficient. According to the modern concept, dental caries results from ecological restructuring of the biofilm and microbial dysbiosis. Metagenomic and metabolomic studies demonstrate that not only microbial composition but also microbial metabolic activity plays a decisive role in the development of dental caries. The increased expression of genes encoding enzymes involved in carbohydrate metabolism, glycosyltransferases, and organic acid synthesis is being investigated as a potential molecular biomarker of dental caries. This may enable early disease detection and the development of personalized preventive strategies. New approaches

based on microbiota modulation, including the use of probiotics, prebiotics, synbiotics, and postbiotics, are considered promising strategies for the prevention of dental caries. Although preliminary clinical studies suggest that these interventions may reduce the abundance of cariogenic bacteria and help restore the ecological balance of the biofilm, large-scale randomized clinical trials are required to confirm their long-term effectiveness.

CONCLUSION

The oral microbiota is one of the central biological factors involved in the development of dental caries. Current scientific evidence confirms that dental caries is not caused by a single pathogenic microorganism but is a polymicrobial disease that develops as a result of disruption of the ecological balance among microorganisms within the biofilm. Dysbiosis leads to an increased proportion of acid-producing and acid-tolerant bacteria, which lowers biofilm pH, accelerates enamel demineralization, and contributes to the development of dental caries. Modern technologies such as 16S rRNA sequencing, metagenomics, metatranscriptomics, and metabolomics enable detailed analysis of the composition and functional characteristics of the oral microbiota. These approaches have considerable potential for the early diagnosis of dental caries, assessment of individual disease risk, and development of personalized prevention programs. Probiotics, prebiotics, postbiotics, and biological agents designed to modulate the microbiome are expected to become important components of dental caries prevention and comprehensive treatment in the coming years. However, multicenter and long-term clinical studies are still required to establish their clinical efficacy conclusively.

PRACTICAL RECOMMENDATIONS

1. In patients at high risk of dental caries, it is advisable to introduce methods for assessing the oral microbiota in addition to routine clinical examination.
2. Preventive programs should incorporate approaches aimed at maintaining the balance of the oral microbiota alongside standard oral hygiene measures.
3. Limiting the intake of fermentable carbohydrates in the diet can reduce biofilm acidification and lower the risk of dental caries.
4. It is advisable to develop clinical protocols for the use of probiotic and postbiotic preparations.
5. In Uzbekistan, molecular genetic research aimed at investigating regional characteristics of the oral microbiome should be expanded.

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